ACTA RADIOLOGICA
EDITA PER SOCIETATES RADIOLOGICAS DANIÆ, FENNIÆ, HELVETIÆ, HOLLANDIÆ, NORVEGIÆ ET SUECIÆ

VOL. XXVI FASC. 5 31 : VIII 1945 N:o 153

A CASE OF ILEOCOLIC INTUSSUSCEPTION REDUCED WITHOUT OPERATION[1]

by

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Until a few years ago it was generally agreed that intussusceptions beginning from the small bowel could not be reduced conservatively. Thus, WICHMANN wrote already in 1893 that »it is probable that it has now and then been possible to force a little air or fluid up through the ileocecal valve, but it is more than doubtful if such a distension of the latter has ever been obtained that it has had any real effect on an intussusception of the small bowel». KOCK & ØRUM believed in 1911 that taxis might sometimes be employed with good result, but they did not adduce any sure proof in support of that statement. ØSTERGAARD CHRISTENSEN wrote in 1934 about ileocolic intussusception: »... this form, which absolutely calls for surgical treatment», and in the same year SJÖSTRÖM wrote that in cases of intussusception of the small bowel surgical operation is clearly indicated. In 1935, JACOBY wrote: »Ileocolic intussusceptions can hardly be reduced by injection of barium under roentgen control»; and as recently as in 1939 LAURELL said in his work on acute abdominal disorders that ileocolic and ileal intussusceptions cannot be reduced.

The first report of an unbloody reduction of an intussusception of the small bowel seems to be one made by EDBERG. It was of the ileocolic type and was successfully reduced by injection of barium enema under roentgen control, but re-formed a week later, whereupon operation was performed, which showed that it had arisen from a diverticulum close to the ileocecal junction. EDBERG's description is not accompanied by illustrations. In 1934, POULIQUEN reported a case in which an ileocolic intussusception was incompletely disinvaginated by injec-

[1] Submitted for publication, March 7, 1945.

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tion of an enema, whereupon palpation under anesthesia completed the reduction. Also here documentation by illustrations is lacking. In NORDENTOFT's large monograph is described a case of ileocolic intussusception which was reduced without operation, as the author writes: »either by barium or spontaneously»; because the case was a chronic, spontaneously recurring one (Figs. 117—118 in NORDENTOFT's work).

HELLMER wrote in 1942, in a paper in the »Röntgenpraxis»: »Die Invaginationen, die vom Dünndarm ausgingen, konnten wir im allgemeinen nicht reponieren.» But already in the following year, 1943, he wrote in an article in the Acta Radiologica: »The method can very well be used for intussusceptum starting in the small intestine», and reported that out of a total of 51 cases of that type he had successfully reduced 30 by the barium method. He only gives documentary evidence for one of them, however, in the form of roentgenograms (his Figs. 13—14), in which it is seen that the invagination began about 6—8 centimeter oral to the ileocecal junction.

Thus, only few cases of conservatively reduced intussusception have hitherto been reported. To these I can add the following.

Case History

Boy, 21 months old, hitherto completely well. Six hours before he was seen, he suddenly became ill, shortly after he had eaten his breakfast with his usual appetite. He vomited several times and had spells of violent crying about every ten minutes. Between these spells he was quiet. Two and a half hours after the onset of the pains, the physician who had been called in administered a large water enema, which was quitted without blood or slime. When seen, he was lying quietly, almost apathetic. Temperature, 36.5; pulse, 120. The tongue moist. Below the right thoracic margin was felt an uncharacteristic resistance. Rectal exploration, nothing abnormal.

Fig. 1.

At the roentgen examination, which was immediately made, the contrast enema was seen to stop anally to the right flexure, and a typical intussusception figure was formed (Fig. 1). The intussusceptum was without difficulty brought back to the cecum (Fig. 2), and the enema now flowed into the small bowel; but there a typical intussusception figure, about 10 cm. long, was seen, which persisted despite several attempts at reduction (Fig. 3). After a fourth attempt, under 1.5 m. fluid pressure and simultaneous cautious manipulation of the abdomen, corresponding to the ileocecal junction, the intussusceptum was suddenly seen to become

Fig. 2.

forced back into the small bowel, whereupon the latter in nearly its entire extent became filled with the contrast fluid (Fig. 4). Two hours afterwards the intussusception figure had not re-formed. The subsequent course was without complications, and on the third day the child was discharged in good condition.

Epicrisis. — We thus have here a case of a boy, 21 months old, who had become acutely ill and was brought in with the usual symptoms of intussusception. The roentgen pictures showed an invagination which had reached to the middle of the transverse colon; and during the reduction under screening-control it was seen that the intussusceptum was rather easily reduced as far as to the ileocecal junction. The small-bowel component could at first not be disinvaginated, but presented itself as a typical intussusception figure about 10 cm. long, surrounded

Fig. 3.

by a thin layer of contrast. Only after three—four vain attempts was the reduction successfully accomplished under a fluid-pressure of about 1.5 m. and simultaneous cautious manipulation of the abdomen over the ileocecal junction. Anesthesia was not employed.

Intussusceptions of the small bowel can thus in some cases be reduced conservatively. With the forms where the invagination begins in the ileum, close to the ileocecal junction, it is even probable that the reduction can be made fairly easily — as HELLMER's report of 30 reduced cases out of 51, cited above, seems to indicate. The former belief that the small-bowel forms were irreducible can partly be explained by the difficulty of distinguishing between an ileocecal intussusception and an ileocolic beginning close to the ileocecal junction, so that all reduced cases were hitherto called ileocecal. This would also explain the fact that several authors have been able to reduce 80 per cent of their cases con-

Fig. 4.

servatively although it is reckoned that 40 per cent of all intussusceptions are of the small-bowel type. About this, NORDENTOFT writes in his monograph as follows:

»The fact is that large published materials of cases either primarily operated upon or verified by postmortem examination show, roundly figured, twice as many small-bowel forms of intussusception as other large materials of cases in which only conservative treatment, or operation secondary to such, has been employed; from which it must be assumed that small-bowel (ileocolic) forms of intussusception were reduced by conservative method, or that the therapeutists who operated primarily have used a terminology different from that of those who employed conservative treatment.»

It is thus probable that a not inconsiderable part of the low situated small-bowel forms can be reduced conservatively. And that the same

is sometimes the case with intussusceptions beginning until 10 cm. from the ileocecal junction is shown both by HELLMER's case and the one here reported. There is therefore reason to try an energetic conservative reduction, also in intussusceptions of the small bowel, before deciding upon operation.

SUMMARY

The author reports the reduction, by conservative methods, of a case of small-bowel (ileocolic) intussusception beginning 10 cm. oral to the ileocecal junction. Only one similar case has hitherto been reported (HELLMER).

ZUSAMMENFASSUNG

Verf. berichtet über mit konservativen Methoden vorgenommene Reposition bei einem Falle von Dünndarminvagination (ileocolica), die 10 cm oral vom Ileozökalwinkel anfing. Es ist bisher nur ein einziger Fall dieser Art beschrieben (HELLMER).

RÉSUMÉ

L'auteur rapporte un cas de réduction d'une invagination (iléocolique) de l'intestin grêle débutant à 10 cm de l'anastomose iléo-cœcale par les méthodes conservatrices. Il n'a été rapporté jusqu'ici qu'un seul cas de la même affection. (HELLMER).

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AUS DER RÖNTGENDIAGNOSTISCHEN ABTEILUNG DES KRANKENHAUSES DER UNIVERSITÄT, LUND, SCHWEDEN (VORSTAND: DR. MED. H. HELLMER)

CANCER COLI MULTIPLEX[1]

von

Olle Olsson

Der Multiplizität maligner Tumoren bei ein und demselben Individuum hat man in der Geschwulstpathologie grosses Interesse gewidmet. Zahlreiche Arbeiten und kasuistische Mitteilungen hierüber sind in dem pathologisch-anatomischen Schrifttum zu finden. Besonderes Gewicht wurde dabei auf die biologische Bedeutung der multizentrischen Geschwulstentstehung gelegt. Um der Besprechung dieser Frage eine sichere Grundlage zu geben, haben BILLROTH, durch die sog. Billroth'schen Postulate, und GOETZE strenge Forderungen für den Beweis einer tatsächlichen Multiplizität der Tumoren aufgestellt.

Multiple maligne Tumoren können in systematisierte oder plurizentrische (BORST), d. h. es befinden sich mehrere Tumoren in demselben Organ oder Organsystem, und nicht-systematisierte Geschwülste, die in anatomisch und funktionell verschiedenartigen Organen auftreten, eingeteilt werden. BORRMAN gibt eine entsprechende Nomenklatur mit den Bezeichnungen, lokale und getrennte Vielfältigkeit, an.

Schon innerhalb der nicht-systematisierten Gruppe kann es schwer sein, eine tatsächliche Multiplizität einwandfrei zu beweisen. Bei den systematisierten Geschwülsten werden die Schwierigkeiten noch grösser. Während somit die vollständige Beweisführung beim Digestionskanal, der ziemlich häufig multiple maligne Tumoren aufweist, schwierig sein kann, ist eine Differenzierung nach den aufgestellten Grundsätzen bei einem einzelnen Organ unmöglich.

Obwohl im Schrifttum multiple Dickdarmtumoren mitgeteilt werden, ist der Beweis für die Multiplizität der Geschwulstzentren keineswegs so sicher, wie es in dem oben Angegebenen gefordert wird. Im Hinblick auf die Fragen, die hier behandelt werden sollen, ist dieses, wie aus dem Folgenden hervorgeht, jedoch kein Nachteil.

Multiple maligne Tumoren werden im Hinblick auf zeitliche Faktoren eingeteilt: Man unterscheidet zwischen synchronen und metachronen Tu-

[1] Bei der Red. am 27. II. 1945 eingegangen.

moren, d. h. die Tumoren sind entweder gleichzeitig vorhanden, oder es vergeht eine gewisse Zeit, z. B. zwischen der Operation eines Coloncancers und dem Auftreten eines weiteren, gleichartigen Tumors. Aus den Angaben im Schrifttum über Fälle der metachronen Gruppe kann man nicht selten ohne weiteres den Schluss ziehen, dass diese in Wirklichkeit der synchronen Gruppe angehörten: die nachträglich entdeckte Geschwulst war schon bei der ersten Untersuchung vorhanden, wurde aber nicht entdeckt.

Von Interesse für die vorliegende Arbeit ist nur die synchrone Gruppe, und innerhalb dieser die systematisierte, auf ein Organ, den Dickdarm, beschränkte. Das Rectum wird in diesem Zusammenhang zum Dickdarm gezählt.

Die Vielfältigkeit von Dickdarmkarzinomen — zum ersten Mal von FENGER, 1888, beschrieben — wird in der pathologisch-anatomischen Literatur einstimmig als ein nicht seltenes Vorkommnis mitgeteilt (HENKE-LUBARSCH: »Primäre Multiplizität von Darmkrebsen insbesondere solchen des Dickdarms ist nicht selten»). Dieses ist nicht erstaunlich, wenn man daran denkt, welche Rolle die im Dickdarm so häufig auftretenden Polypen als praecanceröse Elemente spielen sollen. Angeregt hauptsächlich durch SCHMIEDEN, hat man dieser Frage sehr grosses Interesse gewidmet, und es ist ein umfangreiches Schrifttum über die Bedeutung der Polypose des Digestionskanales für das Karzinom vorhanden. Zahlenmässige Angaben über multiple Coloncancer sind jedoch selten im Schrifttum zu finden. Hier soll für einen späteren Vergleich nur eine Zahl von PAUS angegeben werden, der bei einem Sektionsmaterial von 318 Fällen von Dickdarmkrebs bei 7, d. h. bei gut 2 %, eine Multiplizität fand.

Im Gegensatz zu den Erfahrungen aus dem Sektionsmaterial sind Angaben über eine Multiplizität des Cancer coli auf Grund klinischer Beobachtungen überraschend selten. Bei den meisten grossen klinischen Zusammenstellungen ist überhaupt keine Multiplizität beobachtet worden. PAUS fand nur bei 2 von 571 klinischen Fällen von Coloncancer eine Multiplizität. Dies bedeutet weniger als ½ %, eine wesentlich niedrigere Anzahl als die des Sektionsmaterials desselben Verfassers. Eine Ausnahme bezüglich der Häufigkeit innerhalb klinischen Materials bildet COKKINIS, der bei 4 seiner 54 operierten Fälle von Cancer coli eine Multiplizität fand, die grösste, bisher angegebene Zahl.

Einer der Gründe für die im übrigen auffallend geringere klinische Häufigkeit liegt zweifellos in einer mangelhaften Diagnostik. Eine genauere Diagnostik hätte, wie oben angedeutet wurde, sicher die Fälle synchroner Multiplizität auf Kosten der metachronen Gruppe vermehrt.

Im klinischen Schrifttum werden die Fälle meist in Form kasuistischer Mitteilungen beschrieben. Ihre Veröffentlichung geschieht oft nur, weil

derartige Fälle angeblich selten sind. Werden die Fälle besprochen, so nur unter Berücksichtigung der pathologisch-anatomischen Literatur. Vereinzelt werden allgemeine Gesichtspunkte über die klinische Bedeutung der Multiplizität hervorgehoben. MAINGOT, der damit rechnet, dass die Multiplizität des Cancer coli nicht selten ist, sagt: »To overlook a second growth during a resection for operable carcinoma would be a major catastrophe.» BARGEN und RANKIN sind derselben Ansicht und weisen auf die Bedeutung der Multiplizität, sowohl synchroner wie metachroner Tumoren, für die Prognose hin.

Für die Diagnosenstellung des Coloncarcinoms spielt die Röntgenuntersuchung häufig eine entscheidende Rolle. Es ist deshalb erstaunlich, dass die multiplen Coloncarcinome von röntgendiagnostischen Gesichtspunkten aus überhaupt nicht behandelt worden sind. Die röntgenologischen Hinweise, die man zuweilen bei Fällen der klinischen Literatur findet, zeigen, dass es notwendig ist, die Aufmerksamkeit der Röntgenologen auf das nicht seltene Vorkommen einer Vielfältigkeit des Coloncancers zu lenken.

Der Anlass, aus dem diese Frage jetzt aufgenommen wird, ist, dass wir in den letzten 3 Jahren in der Röntgendiagnostischen Abteilung in Lund nicht weniger als 5 Fälle mit synchronen multiplen Coloncarcinomen untersucht haben:

Fall 1: A. S. Früher Eisenbahnbeamter. 68 Jahre. Chir. Krgsch. 3182/42.

Klinische Diagnose: Cancer coli ascendentis et sigm.

Anamnese: Vater gestorben an Leberkrebs. — Pat. hat seit einigen Jahren dünnen Stuhl 7—8 mal täglich, versetzte Blähungen und Tenesmen. Vor einer Woche etwas Blut im Stuhl. Im letzten Jahr 20 Pfund abgenommen.

Klinische Untersuchung: Bauch: Ø. Per rectum: Ø. Mässige Anaemie. Weber neg.

Röntgenuntersuchung des Dickdarms am $^{29}/_{8}$ 1942: Im distalsten Teil des Colon sigmoideum eine 10 cm lange geringe Lumenverengerung mit unregelmässigen Konturen. Im Colon ascendens, einige cm von der Flexura hepatica entfernt, eine 4 cm lange, zirkuläre, starke Lumenverengerung, deren Begrenzung auf beiden Seiten wallartig ist. *Röntgendiagnose: Cancer coli ascendent. et sigm.* (Abb. 1).

Operation $^{8}/_{9}$ 1942 (STRÖMBECK): Resectio ileo-coecal. + ileo-transversostomi + Vorlegung des oralen Colonstumpfes zur Coecostomie.

Im Colon ascendens ein relativ weicher, etwas stenosierender Tumor, der von der hinteren Wand ausgeht. Ausserdem ist im Colon pelvinum ein bis zwei Querfinger unterhalb des Promontorium ein wahrscheinlich stärker stenosierender Cancer vorhanden.

Fall 2: E. N., Kaufmann. 55 Jahre. Chir. Krgsch. 3555/42.

Klinische Diagnose: Cancer coli dx. inexstirp.

Anamnese: Seit 1 Jahr müde, Abmagerung. Zeitweise Durchfälle, sonst normaler Stuhl.

Klinische Untersuchung: Hb: 32 Ery: 2.48 Millionen. Senkungsreaktion 56/104. Weber: pos.

Bauch: Ø. Per rectum: Ø.

Abb. 1. Fall 1.

Röntgenuntersuchung des Dickdarms am $^{25}/_{9}$ 1942: Im rechten Teil des Colon transversum eine 3 cm lange, starke Lumenverengerung. An der Spitze der Flexura hepatica eine ähnliche, etwas längere Lumenverengerung. *Röntgendiagnose: Zwei Coloncancer im Gebiet der Flexura hepatica.*

Operation $^{6}/_{10}$ 1942 (STRÖMBECK): Ileo-transversostomie. Doppelt faustgrosser Cancer, der die Flexura hepatica und den angrenzenden Teil des Colon transversum befallen hat. Ob es sich um einen oder zwei Tumoren handelt, kann nicht beurteilt werden. Die Geschwulst ist inoperabel.

Fall 3: A. P., Früher Bauer. 72 Jahre. Chir. Krgsch. 55/43.

Klinische Diagnose: Cancer recti et coli sig.

Anamnese: Seit 10 Monaten Obstipation, Stuhl mit Blutstreifen, in der letzten Zeit Tenesmen und Schmerzen bei der Defäkation, Abmagerung.

Klinische Untersuchung: Hb. 50, Ery: 3.8 Millionen. Senkungsreaktion 16/34. Weber abwechselnd positiv oder negativ.

Bauch: In der Fossa iliaca eine bewegliche, 15 cm lange wurstförmige Resistenz palpabel. Rectal ist ein harter Tumor palpabel.

Röntgenuntersuchung des Dickdarms $^{27}/_{11}$ 1942: In der Ampulla recti am Anus eine 5 cm lange, unregelmässig begrenzte Lumenverengerung. Im mittleren Teil des Colon sigmoideum, ca 40 cm vom Anus entfernt eine ähnliche Verengerung, die 5 cm lang ist, und auf beiden Seiten eine wallartige Begrenzung hat. *Röntgendiagnose: Cancer recti et coli sigmoidei* (Abb. 2).

Operation am $^{10}/_{12}$ 1942 (STRÖMBECK): Amputatio recti abdominosacralis erster Teil + exstirpatio canceri sigmoidei. In der Mitte der beweglichen Flexura sigmoidea ein ringförmiger, einige Zentimeter langer, stark strikturierender scirrhöser Cancer. Im Rectum ein fast zirkulärer Tumor.

Abb. 2. Fall 3.

Fall 4: E. H. Witwe. 68 Jahre. Chir. Krgsch. 991/43.

Klinische Diagnose: Cancer coli.

Anamnese: Seit 15 Jahren Magenbeschwerden. Schmerzen im Epigastrium, kann keine fetten Speisen vertragen. Aufgetriebener Leib und Obstipation. Seit mehr als einem Jahr Abmagerung, Müdigkeit, Schwindel, Darmtenesmen.

Klinische Untersuchung: Hb. 42, Ery: 3.65 Millionen. Senkungsreaktion 36/74. Weber pos.

Bauch: Ø, per rectum: Ø.

Röntgenuntersuchung des Dickdarms $^{22}/_{2}$ 1943: Im Colon sigmoideum eine 10 cm lange, zirkuläre Infiltration mit rectalwärts wallartiger Begrenzung. Im rectalen Teil des Colon descendens eine ähnliche, etwas kürzere Lumenverengerung, die oralwärts wallartig begrenzt ist. Die veränderten Darmbezirke liegen neben einander, ihrer Lage entsprechend ist eine Resistenz palpabel. *Röntgendiagnose: Cancer coli sigmoidei et descendentis* (Abb. 3).

Operation am $^{8}/_{2}$ 1943 (Wulff): Coecostomie. Schon beim Anlegen der Lumbalanaesthesie kann man unter den Bauchdecken eine Darmschlinge erkennen. Bei der Laparotomie zeigt sich, dass deren Schenkel durch einen faustgrossen Tumor mit

Abb. 3. Fall 4.

einander verwachsen sind. Bei einem späteren Eingriff zwecks dessen Entfernung erweist sich der Tumor als inoperabel.

Fall 5: A. H., Kaufmann. 69 Jahre. Chir. Krgsch. 1945/44.

Klinische Diagnose: Cancer coli sigmoidei et cancer coli flexuræ hepat.

Anamnese: Seit 30 Jahren Diabetes mellitus. Vor 1 Jahr wurde eine essentielle Hypertonie festgestellt. Seit $^1/_2$ Jahr ist Pat. müde und hat schlechten Appetit. Seit 4 Monaten Obstipation und in der letzten Zeit 4—5 mal täglich Stuhldrang. Etwas abgemagert.

Klinische Untersuchung: Hb. 74, Ery. 3.8 Millionen. Senkungsreaktion 81/113.

Röntgenuntersuchung des Dickdarms. $^{20}/_4$ 1944: An der Übergangsstelle des Colon descendens zum sigmoideum eine 6 cm lange, starke Verengerung des Darmlumens, die auf beiden Seiten wallartig begrenzt ist. Dem Röntgenbefunde entsprechend ist eine verschiebbare Resistenz zu fühlen. Die Sigmoideumschlinge ist ziemlich lang. *Röntgendiagnose: Strikturierender Cancer coli.*

Operation am $^{3}/_{5}$ 1944 (STRÖMBECK): Probelaparotomie + Coecostomie. Etwas oberhalb der Mitte des Colon sigmoideum ein 5 cm langer, zirkulärer Tumor.

Nach der Operation anhaltendes Fieber. Am $^{12}/_{6}$ 1944 Exitus infolge einer Lungenembolie.

Obduktion $^{13}/_{6}$ 1944 (Obd. Nr. 250/44) (E. SJÖVALL): Path. Anat. Diagnose: Doppelter Coloncancer (Flex. sigm. + Flex hepat.). Colon: In der Mitte des Colon sigmoideum ein gänseeigrosser, zirkulärer Tumor, der einen 10 cm langen Bezirk der Colonwand infiltriert. Die Flexura hepatica enthält einen gleichen zirkulären, aber halb so grossen Tumor.

Im Hinblick auf die oben angeführten Angaben im Schrifttum geben die referierten Fälle Anlass zu Betrachtungen aus röntgendiagnostischen Gesichtspunkten. Wie erwähnt ist die Entscheidung, ob es sich um eine wirkliche Multiplizität handelt, bei den meisten Fällen der Literatur ebenso wie in diesem Fall nicht mit Sicherheit möglich. Es sind zwar Fälle beschrieben worden, bei denen mikroskopisch deutliche Unterschiede zwischen den Tumoren zu finden waren, also eine Multiplizität nachgewiesen worden ist. Dazu kommen jedoch Fälle, bei denen die Multiplizität nebeneinander liegender Tumoren z. B. durch eine Propagierung via die Lymphbahnen und einem erneuten Durchbruch in die Mucosa bedingt ist. Ferner besteht die Möglichkeit dass einer der Tumoren eine canaliculäre Implantationsmetastase darstellt. Für die hier zu behandelnden Gesichtspunkte spielt dieses keine Rolle: Gleichgültig wie die Multiplizität entstanden ist, hat sie im Hinblick auf röntgenologische und andere, im Folgenden zu besprechende Gesichtspunkte, dieselbe Bedeutung. Für die Röntgenologie wird die Wichtigkeit dieser Frage dadurch noch mehr hervorgehoben, dass auch diejenigen Fälle besprochen werden, bei denen die Multiplizität mehr ein topographisches als ein biologisches Phänomen darstellt.

Unter den zahlreichen kasuistischen Mitteilungen multipler Coloncancer ist die häufigste Kombination die eines Carcinoms im Rectum und eines in einem der übrigen Abschnitte des Dickdarms wie z. B. bei dem oben referierten Fall 3. Diese Kombination ist im Hinblick darauf, dass das Rectumcarcinom unter denen des Verdauungskanales am häufigsten auftritt, ebenso häufig wie alle übrigen Carcinome des Digestionskanales zusammen, nicht sehr erstaunlich. BARGEN und RANKIN teilen 14 Fälle multipler synchroner Dickdarmgeschwülste mit, von denen die Hälfte die erwähnte Kombination zeigte. Zu derselben Gruppe gehören 4 Fälle von GABRIEL und Fälle, die von ABEL, MAINGOT, NORBURY u. a. beschrieben wurden. Im übrigen kommen alle Kombinationen und verschiedene Grade der Multiplizität vor.

Die häufige Kombination mit einem Rectumcarcinom erfordert besondere Aufmerksamkeit. Das Rectumcarcinom wird im allgemeinen digital und proctoscopisch diagnostiziert und gibt meist keinen Anlass zu einer Röntgenuntersuchung des Dickdarms. Im Hinblick auf das geschil-

derte relativ häufige Vorkommen weiterer Dickdarmcarcinome sollte eine derartige Untersuchung jedoch vorgenommen werden. Bei 2 der 4 Fälle von GABRIEL fand man bei einer »preliminary laparotomy» wegen eines palpatorisch festgestellten Rectumcarcinoms einen Cancer im Colon sigmoideum. Der dritte Fall betrifft einen Patienten, bei dem ein Rectumcarcinom diagnostiziert worden war. Dieser bekam einen akuten Ileus, der, wie sich bei der Laparotomie zeigte, durch einen Cancer im Colon transversum bedingt wurde. Der letzte Fall endlich bekam am 36. Tage nach einer Operation wegen eines Cancer recti einen Ileus, der, wie die Laparotomie ergab, durch einen Krebs des Colon transversum hervorgerufen worden war.

Aus den oben angegebenen Tatsachen ergibt sich für den Röntgenologen, dass er beim Rectumcarcinom nicht nur die Aufgabe hat, die obere Grenze des Tumors zu bestimmen (zu diesem Zweck wird der Pat. oft zur Untersuchung geschickt), sondern eine vollständige Colonuntersuchung vorzunehmen. Eine andere Teiluntersuchung, mit der sich der Kliniker und Röntgenologe beim Rectumcarcinom zuweilen begnügt, ist die Feststellung der Länge des Sigmoids. Dieses kann aus operationstechnischen Gründen wertvoll sein, der Röntgenologe darf aber die Untersuchung wegen einer derartigen Fragestellung nicht einschränken.

Gleichgültig ob ein Rectumcancer diagnostiziert wurde, oder der Untersucher einen anderswo lokalisierten Krebs gefunden hat, muss die Untersuchung sorgfältig und mit voller Aufmerksamkeit bis zu Ende durchgeführt werden, denn es können ernste Folgen eintreten, wenn ein anderer vielleicht vorhandener Tumor übersehen wird. Hier soll auf Fall 5 hingewiesen werden, bei dem nur der distale Tumor diagnostiziert wurde.

Einige Untersucher pflegen die Untersuchung, wenn ein Cancer coli diagnostiziert worden ist, mit der Begründung abzubrechen, dass der Darm oralwärts von der veränderten Darmpartie nicht durch Kontrast belastet werden soll. Dieses Verfahren, das bei akuten Ileusfällen notwendig ist (HELLMER), ist bei den übrigen Fällen nur dann gerechtfertigt wenn eine schwer durchgängige Stenose des Darmlumens vorhanden ist. Bei derartigen Fällen kann die Möglichkeit nicht ausgeschlossen werden, dass ein Ileus erzeugt wird, obwohl man über die Passage nicht zu weitgehende Schlüsse aus der Tatsache ziehen kann, dass die Einführung eines Kontrastmittels in retrograder Richtung erschwert ist. Wird aber dieses Verfahren angewandt, so soll der Kliniker darüber unterrichtet werden, dass nur eine unvollständige Untersuchung vorgenommen worden ist.

Bei akuten Ileusfällen, bei denen eine Dickdarmuntersuchung vorgenommen wird, muss der Untersucher die Befunde der Leeraufnahmen mit denen bei der Kontrasteinführung vergleichen und sich ein Urteil

darüber bilden, ob die bei der späteren Untersuchung gefundene Stenose die Veränderungen, die vorher gefunden wurden, ausreichend erklärt. Diese Vorsichtsmassnahme ergibt sich aus der Tatsache, dass akute oder subakute Ileusattacken so oft zu den Erscheinungen des Coloncarcinoms gehören. CRAFOORD gibt als Initialsymptom bei 22.5 % seines Materials von 161 Fällen ein Darmhindernis an, und nicht weniger als 63 % seiner Patienten hatten anamnestisch Ileuserscheinungen. PETRÉN findet bei seinem Material von 50 Patienten, dass $^2/_5$ der Fälle als akute Bauchfälle in die Klinik eingeliefert wurden, 9 davon als akuter Ileus. SÖDERLUND findet unter 152 Fällen bei 40 % einen akuten Ileus in der Anamnese. JOHNSSON stellt bei 57 % von 164 Fällen von Coloncancer Erscheinungen eines Darmhindernisses fest. Nicht weniger als 17 % der Fälle seines Materials wurden unter dem Bilde eines akuten Ileus in das Krankenhaus eingeliefert.

Eine röntgenologische Dickdarmuntersuchung stellt in der Regel grosse Anforderungen an den Untersucher. Die hier mitgeteilten 5 Fälle gehören zu einem Material röntgenologischer Coloncancer, das pro Jahr 50—60 Fälle enthält, die ihrerseits aus einem Untersuchungsmaterial von jährlich 700—800 Colonuntersuchungen stammen. Aus diesen Zahlen ergibt sich, wie sorgfältig derartige Untersuchungen durchgeführt werden müssen. Sie zeigen fernerhin, dass die Multiplizität des Coloncarcinoms kein besonderes seltenes Vorkommnis ist. MÜLLER, der unter 5,012 Sektionsfällen 1,121 Carcinome sah, von denen 18 multipel auftraten, hat aus der Häufigkeit der Multiplizität innerhalb verschiedener Altersgruppen berechnet, dass die Wahrscheinlichkeit eines Doppelcancers mit dem Quadrat der Carcinomfrequenz zunimmt. Er fand im 5. Dezennium einen, im 6. vier und im 7. und 8. Dezennium 6 Fälle mit einer Multiplizität. Diese Zahlen, die sich auf die Multiplizität des Krebses im allgemeinen beziehen, unterstreichen die Bedeutung des Besprochenen, da wir zweifellos damit rechnen müssen, dass die Häufigkeit dieser Fälle in demselben Masse zunehmen wird, in dem die Indikationen für die Krankenhausbehandlung und damit auch für die Röntgenuntersuchungen der Alterserkrankungen erweitert werden.

ZUSAMMENFASSUNG

Durch die Zunahme der Krankenhausbehandlung und damit auch der Röntgenuntersuchung der Patienten höherer Altersgruppen werden die klinischen Fälle mit synchron auftretenden multiplen Dickdarmkrebsen immer häufiger. Ihre Kenntnis ist deshalb wichtig bei Röntgenuntersuchungen dieses Organs. Der Verf. gibt an, unter welchen Umständen der Röntgenologe seine Aufmerksamkeit hierauf besonders richten muss.

SUMMARY

Clinical cases of combined multiple cancer of the large intestine have become more common owing to an increase in hospital treatment and, consequently, to an increase in roentgen examination of patients belonging to the older age-group. The diagnosis of these is therefore of the greatest importance when roentgen axamining the intestines. The author points out circumstances which roentgen specialists should give their special attention to in the said occurrences.

RÉSUMÉ

Le nombre des cas cliniques de cancers multiples et simultanés du colon augmente parallèlement à l'accroissement du nombre des traitements hospitaliers de malades âgés et du nombre correspondant d'examens radiologiques. C'est pourquoi il est important de pouvoir les reconnaître lors de l'examen radiologique de cet organe. L'auteur indique dans quelles circonstances le rœntgenologue doit porter spécialement son attention sur ce point.

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FROM THE MEDICAL CLINIC OF THE ROYAL UNIVERSITY AT LUND
(DIRECTOR: PROFESSOR SVEN INGVAR)

TUMOURSIMULATING INTRATHORACIC HETEROTOPIA OF BONE MARROW[1]

by

Erik Ask-Upmark, M. D.

Introduction

In adults haematopoiesis is confined to the red bone marrow, i. e. to the bones of the trunc, the head and the proximal ends of humerus resp. femur. In response to a demand for more blood cells, as in cases of severe anemia, the red bone marrow is liable to expand including also the bones of the extremities. If the bone marrow for some reason is unable to comply with the demands (as for example in the marble bone disease) blood formation may be established in the spleen and the liver, to a certain degree also in the kidneys and the lymph nodes, i. e. regions adapted to haematopoiesis during the intra-uterine stage. The foci hence encountered are as a rule of microscopical character, occasionally however to be identified with the naked eye. In certain rare instances, finally, the formation of macroscopical tumours representing ectopic bone marrow has been encountered. Such massive tumour-like bone marrow masses have been observed in falx cerebri, in the thoracic cavity, in the retroperitoneal space and in the pelvis. These observations have been extremely rare and have as a rule been reported by pathologists. To the best of our knowledge no such case has hitherto been identified with regard to its character before autopsy was secured, although in a few instances the diagnosis was obtained on examination of the tumour, removed by operation. This study will attempt to present a case of heterotopic bone marrow, where the diagnosis of the »tumour» was established more than 4 years prior to the death of the patient and eventually confirmed by necropsy.

[1] Submitted for publication, March 23, 1945.

Review of literature

Extramedullary haematopoiesis may generally be encountered under the following conditions:

I. As a normal phenomenon in newborn and infants, where blood forming foci have been observed in the broad ligaments (BRANNAN 1927), in the breasts (DIETRICH 1925, BRANNAN), in the soles and palms (DIETRICH), in prostata, epididymis, kidney, and pelvis renalis (references with DIETRICH).

II. As a pathological phenomenon in infants and adults with the following conditions.

1. In connection with leukemia, where blood forming foci are to be registered in liver, spleen, lymph nodes etc., as well as in haemangioendotheliomas, where clusters and foci of nucleated red cells belong to the picture.

2. In connection with foci of heterotopic bone, wherever be its localization: in bone metaplasia of the tonsils, in old calcified tuberculous lymph nodes, in a calcified aorta, in larynx, and elsewhere. Particular attention should be called to the liability of bone formation and subsequent development of marrow in the urinary tract, as demonstrated experimentally by SACERDOTTI and FRATIN (1901) and by MAXIMOW (ligation of the kidney vessels in rabbits induced the evolution of bone in pelvis renalis) and by LUCINESCO and LERICHE and others (transplantation of part of the mucosa of the urinary bladder into muscular tissue will result in bone formation).

3. Microscopic foci of extra-medullary bone formation may be observed in liver, spleen, kidneys, lymph nodes when the abilities of the bone marrow to meet increased demands of blood cells are insufficient, as in severe anemias during childhood or in adults when neoplastic tissue or osteosclerosis is encroaching upon the territory of the marrow. BRANNAN, where references are to be had, maintains that the myeloid reaction was, in infants, particularly pronounced in lymph nodes and kidneys, occasionally also spleen and thymus, whereas in adults the liver and the spleen were especially important organs; in the spleen the hematopoietic tissue may appear as small red patches; myeloid activity was occasionally observed in organizing thrombs of the broad ligament veins (BRANNAN) and in the pleura (WADE, quoted by BRANNAN).

4. Massive deposits of heterotopic bone marrow, simulating tumour growths have been encountered in the following instances.

a) In dura mater in one case reported by BRANNAN, concerning a male infant aged $7^1/_2$ months who had been suffering from anemia splenica

infantis. The necropsy revealed that falx cerebri had been converted into a thick, dark purplish red and fleshy septum, microscopically identified as bone marrow. Moreover, there was splenomegaly, hepatomegaly, enlargement and reddishness of several lymph nodes and masses of bone marrow in the renal hilus (vide infra).

b) In the thoracic cavity as large, paravertebral growths, representing heterotopic marrow, beneath the parietal pleura in the costovertebral angles. Such masses have been described by SALEEBY (1925), PLONSKIER (1930), LORD DAWSON (1931), HARTFALL and STEWART (1933) and are referred to as having been observed also by RICH at the Johns Hopkins' (one case quoted by BRANNAN) and by DONALD HUNTER (two cases, quoted by HARTFALL and STEWART). In all seven or eight such cases have been recorded, all of them by pathologists. To this group will be returned in connection with the description of my own case.

c) In the retroperitoneal space mainly in connection with the kidneys or the adrenals, occasionally elsewhere. Massive growths of heterotopic marrow, somewhat resembling splenic pulp have been observed distending the hilus of the kidneys in infants with severe anemia, mostly of the von Jaksch type and with rickets. References will be found in the beautiful study of BRANNAN, who himself observed one such case and recollected those reported in the literature, the first case being reported by v. GIERKE (1905). Adrenal tumours composed of elements of bone marrow tissue have been repeatedly described: thus, COLLINS (1932) observed one case and recollected earlier publications on the subject; similar observations have later been made by RICHARDSON (1935) and BOSSELMAN (1937). The suprarenal tumour-like deposits as a rule concerned adults. Retroperitoneal tumours with evidence of blood-forming activity have been described by HOFSTÄTTER and SCHNITZLER (1926) and by WARREN (1928). The studies of PETRI (1925) and VON SOOS (1933) have been of importance for the interpretation of these observations. OBERLING and GUÉRIN (1934) described the formation of heterotopic bone marrow with tumoural aspect in 8 chickens, the growths being situated close to the lower pole of the kidney.

d) Extramedullary hematopoiesis appearing as a massive tumour has finally been recorded between the hollow of the sacrum and the rectum by BLAISDELL (1933, large globoid tumour, surgically removed), by KUDLICH (1935, walnut-sized tumour, occasionally encountered at the autopsy) and by LYALL (1935, fist-sized tumour in a female case of pernicious anemia, as observed at the necropsy).

Briefly summarizing, massive deposits of heterotopic bone marrow simulating tumour growth have been observed occasionally in the retroperitoneal space; on some few instances in the thoracic cavity and once

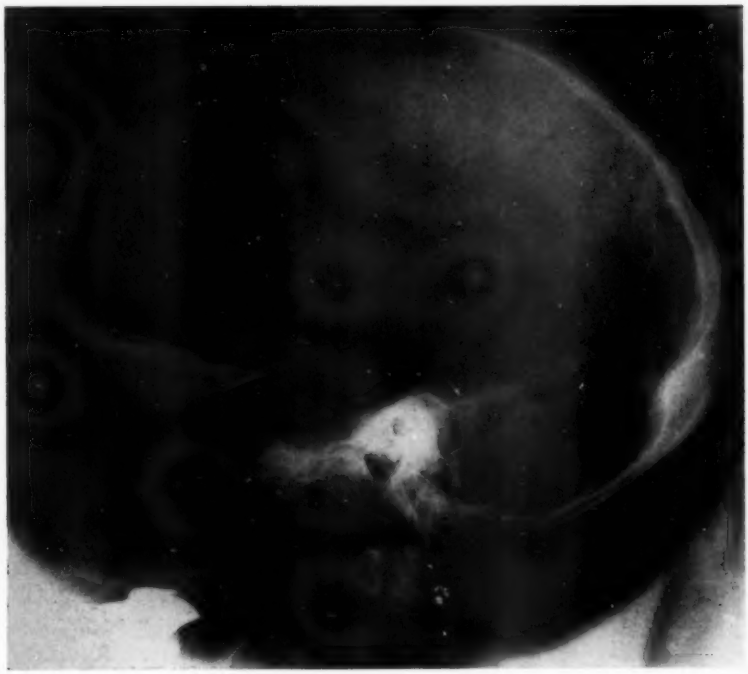


Fig. 1. Radiogram of the cranium June 6th 1940, when the patient was 65 years of age. Multiple areas of reduced density and a somewhat punched-out appearance are to be seen.

within the cranial cavity. The present study will deal with the intrathoracic localization.

Case report

Med. Clin. 358/1945. Woman, aged 70. Observed in the clinic May 10th 1940—June 17th 1940 and Jan. 18th 1945—Jan. 20th 1945. Haemolytic jaundice + Paravertebral heterotopic bone marrow + Cholelithiasis. Final disorders: ileus, pulmonary oedema.

Family history of no interest. Unmarried, no children, has always been doing hard work with washing and suchlike. As far back as she can remember her tint has been yellowish, more so in springs and falls and when catching a cold; pruritus has never been experienced. When aged 38 (in 1912) she was for some time very weak and tired, being almost unable to walk; she was observed in a rural hospital where anemia and »weak red cells» were registered. Afterwards she was able to carry on fairly until the age of 64 (in 1938), when she became hampered by epigastric pains, vomiting and increased jaundice; she stayed in bed for a fortnight and eventually recovered. When aged 66 (in 1940) the

Fig. 2. Radiogram of the chest June 17th 1940. The tumour-like mass at the right side of the VII—IX thoracic vertebrae is easily to be seen. The corresponding deposit at the left side is hidden behind the heart.

same symptoms reappeared: pains in the epigastrium, severe vomiting and increased jaundice; after a fortnight she had a chill and pains in the right side of the thorax. She was admitted to the medical clinic (record 1330/1940) on May 10th and observed forthwith until June 17th.

On admittance she was found to be meagre and with impaired general condition. The temperature was 40 C°, the pulse rate 120, the sedimentation rate (Westergren method) 49, the blood pressure 110/65. There was a considerable jaundice and also some cyanosis and hyperpnoea. Local bed-side observations were from the thorax a dullness of the base of the right lung, from the abdomen an enlarged spleen, reaching some 5 cm below arcus costarum. The blood morphology was as follows: — hemoglobin 78, red cells 3.86 millions, white cells 27,900, differential count: — neutrophils 85 %, lymphocytes 14 %, monocytes 1 %. The average diameter of the red cells was 6.6 μ, there was a reticulocytosis of 48 ‰, the osmotic resistance of the red cells was considerably reduced (0.90 %—0.34 %). The bilirubin was on admittance 3.5/200,000, with a prompt direct reaction; a few days later it was only 0.6/200,000. The serum protein (examined June 13th) was 6.8 %. Sternal puncture revealed an essentially normal picture, no plasmacellular aggregates being possible to identify. The subsequent course in the clinic was complicated by an acute otitis but otherwise she made a fairly rapid recovery but for the anemia which remained essentially unaffected.

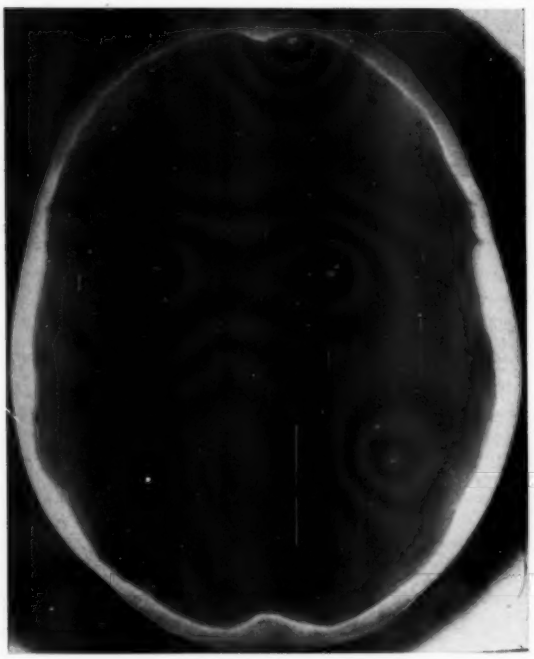


Fig. 3. Radiogram of the calvaria post mortem Jan. 1945. The disseminated rarefications and punched-out areas should be observed.

Roentgenological examination was performed June 3rd, yielding a most remarkable result. In the thorax there was a somewhat elliptic density of the size of 4.5 × 7 cm, situated immediately to the right of the thoracic vertebrae VII—IX. Neither in these vertebrae nor in the connected ribs was anything abnormal to be seen. In the calvaria as well as in the pelvic bones (most so ossa ilei) areas of reduced density were to be seen, which almost attained a punched-out appearance. The thoracic and lumbar spine, the right femur, tibia and fibula, the left humerus, radius and ulna, the bones of the right hand and those of the left foot were examined but did present entirely normal conditions.

The syndrome hence observed might seem a little embarrassing, the possibility of a malignant tumour being perhaps rather difficult to exclude. Nevertheless the interpretation was given by us that the patient did represent a case of acholuric jaundice, that the punched-out areas in the bone system were due to a compensatory proliferation of the marrow and that the paravertebral tumour-like aggregates in thorax did represent heterotopic bone marrow, as observed by solitary pathologists but hitherto never clinically identified. Splenectomy was suggested but declined by the patient. She went home and carried on for the next few years, although repeatedly hampered by periods of abdominal discomforts, nausea and increased jaundice with fever. Such a period eventually appeared Jan. 14th 1945, and she was sent to the surgical clinic by a practitioner with the diagnosis cholelithiasis + ?. On Jan. 18th she was transferred to the medical clinic.

Her general condition was now pretty bad with considerable jaundice but also cyanosis, general exsiccation, temperature 37.2 C°, pulse rate 92, abdomen soft but with a diffuse tenderness. Her non-protein N was 154. Fluids were forced and stimulation given but she went rapidly down-hill and died Jan. 20th.

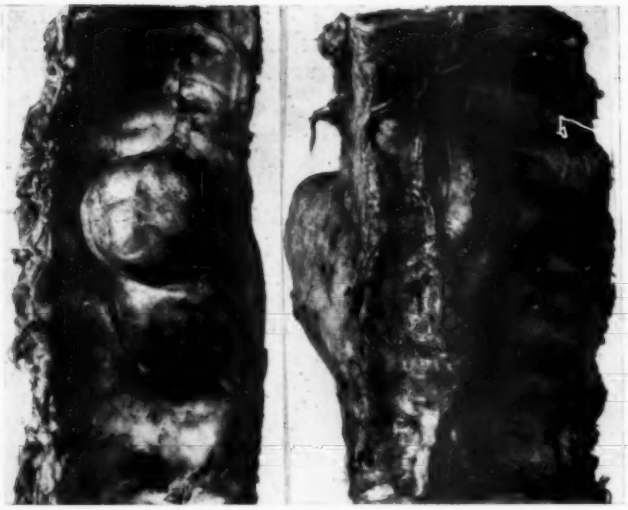
Necropsy was performed in the department of Pathology by professor AHLSTRÖM, who has kindly put the material at my disposition. The following positive observations were taken to the records.

1) Terminal pulmonary oedema. Ileus, due to strangulation of jejunoileum by a cord between two parts of the ileum. Adhesion of one of the bowels to the abdominal wall. Appendix is adhesive to ileum, its apex being clubbed and cicatrized. Some 130 ml muddy haemorrhagic fluid in the peritoneal cavity. A moderate arteriosclerosis of the aorta. Nephrosclerosis.

Fig. 4. Radiogram of the thoracic spine and adjacent part of the ribs, as removed by necropsy. The paravertebral densities are to be recognized. It should be observed that the cortical structure of the vertebrae is entirely unimpaired by the paravertebral masses.

2) The spleen is considerably enlarged (800 Gm), soft, with a red and dry cut-surface; the Malpighian corpuscles are scarcely to be identified. The liver was moderately enlarged (1 830 Gm), dark brown, of dense consistence. Some small pigmented concrements are to be found in the duodenum. The choledochus is moderately distended, the gallbladder hardly as large as a pigeon's egg, cicatrized and with a white and soft mucous membrane. In the hepatic duct, immediately above the confluence an obturating black pigment stone was encountered, approximately as large as the end of the 5th finger. Smaller concrements are to be found in the larger branches of the hepatic duct, which are hardly distended. — The bone marrow of the right femur is everywhere brilliantly red. In the calvaria several small, star-formed, bluish spots are to be noted where the bone is thin and now and then transparent.

3) In the thoracic cavity two large paravertebral masses are to be observed, situated closely adherent to the surface of the spinal column about in the middle of the thoracic spine. The mass on the right side is about goose-egg-sized, that on the left side about hen-egg-sized. The consistence is rather soft, the surface is even or somewhat nodular, the colour is bluish red, topographically the masses are covered by the parietal pleura and laying upon the lateral surface of the bodies of the vertebrae, and the corresponding transverse processes, heads and angles of ribs and intercostal spaces. The cut surface is homogeneous, dark-red, resembling that of the bone marrow or of the spleen. The



a. *b.*

Fig. 5. Macroscopical appearance of the paravertebral masses *a*) seen from the right, *b*) from before and the left. The somewhat hour-glassed appearance is no doubt due to the segmental origin.

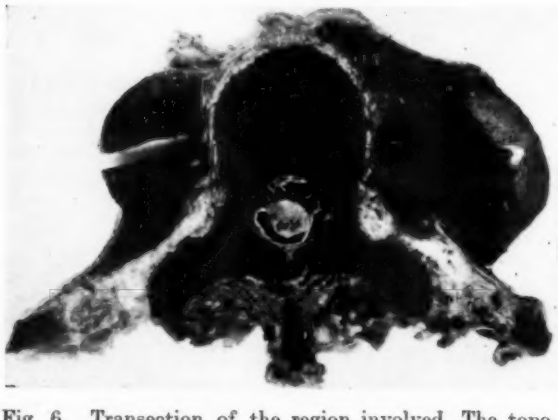


Fig. 6. Transection of the region involved. The topography of the paravertebral deposits is to be recognized, as well as the absence of any connection between the bone marrow of the vertebral bodies and the heterotopic masses.

bodies of the vertebrae are entirely unaffected by the masses, being separated from them by the cortical bone and the ligaments. Besides these large masses there are on both sides small, double pea-sized similar bodies in the collagen tissue of the costovertebral angles.

4) The histological analysis of the *spleen* showed all the characters of hemolytic jaundice, with the red pulp crowded by red blood cells, swollen endothelial cells of the sinus and transformation of the sinus into narrow tubes. The white pulp is of normal appearance. In the red pulp there are disseminated foci of obvious hematopoietic character. The *liver* is of normal structure, with scanty infiltration of round cells in the portal tissue and a moderate storage of iron pigment within the cells of the liver. The *kidneys*

show a pronounced arterio- and arteriolosclerosis, but nowhere any hematopoietic foci. The *bone marrow* is constituted by the normal cells of the erythropoietic and the myeloic systems, the former elements by far dominating. The *paravertebral bodies* show a tissue most similar to that of bone marrow in the stage of hyperactivity. The cellular elements belong to the erythropoietic and the myeloic systems. Hence, red blood cells, normoblasts and other cells of the erythropoietic system are crowded with numerous haemocytoblasts and some megakaryocytes. Myeloic cells are represented in all stages up to and including ripe leucocytes but the erythropoiesis is domineering. The masses are covered with hyalin, connective tissue.

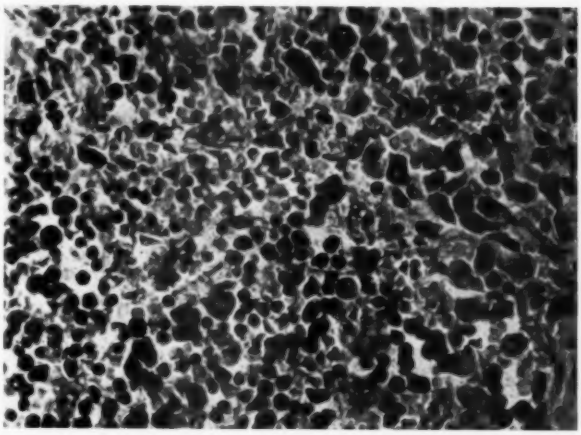


Fig. 7. Microphotogram of the tissue of the paravertebral bodies reveals normal bone marrow in the stage of hyperactivity.

Comment and discussion

The observation described above entails the following questions:

1. The etiology of the tumour-like growth.
2. The formal origin.
3. The clinical conclusions to be derived.

ad (1) *The etiology.*

The massive deposit of heterotopic bone marrow is no doubt to be considered as a compensatory adjustment to meet the increased demand for red blood cells. The existence of such a demand is substantiated on the one hand by the fragility and destruction of the blood corpuscles inherent to the disorder in question, on the other hand by the presence of a hyperplastic bone marrow and of the microscopic haematopoietic foci in the spleen. Additional evidence is to be obtained from the scanty material of similar instances earlier recorded, which will be reviewed as follows.

1. Saleeby (1925): Female, aged 81. »Past history nothing of importance». General arteriosclerosis, right hemiplegia, bronchopneumonia. Heart hypertrophied (570 Gm). Spleen enlarged (405 Gm). Gall bladder

filled with gall stones. Pituitary adenoma. Bone marrow apparently not examined. On each side of the thorax at the fifth rib near the vertebral column a small, reddish, smooth, encapsulated mass (diameter 2.5 cm) adherent to the ribs with fibrous tissue. Microscopy of these masses: slightly hyperplastic normal bone marrow structure; iron stain positive (Prussian blue reaction).

2. SALEEBY (1925): Coloured female, aged 21. Antemortem report in 1922 by YOUNG and COOPERMAN. Osteitis fibrosa cystica generalisata Engel-Recklinghausen. Necropsy performed by SALEEBY: »In the thoracic cavity arising from the parietal pleura a large rounded mass, reddish and measuring about 6 cm in diameter was noted. Though adherent to lung substance with fleshy bands and spicules of bone it had probably arisen from the rib.» Microscopy showed a typical hyperplastic bone marrow structure, containing the various cellular elements of the marrow parenchyma, with the exception of the giant cells which were a predominant feature in the sections of the bone marrow proper.

3. RICH (quoted by BRANNAN 1927): Male individual with acholuric jaundice. Post mortem: kidney-sized tumour masses of bone marrow were found within the thorax. The spleen had been removed some time before death.

4. PLONSKIER (1930): Female, aged 70, died of ulcerating adenocarcinoma of the lesser curvature of the stomach. Marked general anaemia before death. Metastases in the liver and the lymph nodes around v. porta and aorta. Marked hyperplasia and hemosiderosis of the bone marrow. Spleen enlarged (1,300 Gm), extremely hemosiderotic. Paravertebral, subpleural masses, hazel-nut-sized—hen-egg-sized, with no connection to the underlying vertebra; the masses were typical bone marrow, rather much loaded with hemosiderin.

5. LORD DAWSON (1931): Female, aged 53. (Case Labourne.) Acholuric jaundice since girlhood. Severe anaemia. Necropsy: spleen enlarged ($2^1/_2$ lb), cut surface with a rich dark-red pulp, liver enlarged ($5^1/_2$ lb), gall stones, kidneys gave marked reaction for free iron. Bone marrow throughout rich and red, even in the tibia. »Beneath the parietal pleura in the costovertebral angles and of the left side of the sixth to tenth thoracic vertebrae were four nodules of ectopic marrow — — in close contact with bone, and showed a rugged surface when dissected from it.» Histologically the ectopic marrow was strikingly active with numerous mitoses erythroblastic more than leucoblastic.

6. HARTFALL and STEWART (1933): Female, aged 52. Acholuric jaundice, obviously since decades. Considerable anemia. Died from blood transfusion. Hyperplasia of bone marrow. Spleen enlarged — — on section firm, solid, reddish. A large reniform mass of dark maroon colour lay upon the right lateral surface of the 7th to 9th dorsal vertebrae and

the corresponding transverse processes and angles of ribs, a somewhat smaller similar mass was present on the left side opposite the 8th and 9th dorsal vertebral bodies. The parietal pleura was covering these masses which were completely circumscribed without any communication with the marrow of adjacent ribs or vertebrae. On microscopy the heterotopic tumours show the structure of actively erythroblastic bone marrow.

7, 8. HUNTER (quoted 1933 by HARTFALL and STEWART). Two cases of anaemia with massive heterotopia of bone marrow, with the same anatomical location as in the case described by HARTFALL and STEWART.

It will be seen that in the vast majority of the reported instances anaemia was to be registered. Such was the case in the cases (2), (3), (4), (5), (6), (7), and (8) as well as in my own case. With regard to case (1) no anaemia was taken to the records but it should be observed on the one hand that the clinical data in this case are very scanty, the patient being aged 81 and observed for just one week before death, on the other hand that the anatomical observations by no means rule out the possibility of an anaemia: the bone marrow was not examined and the coincidence of ample deposits of blood pigment with splenomegaly and gall stones is anyway entirely compatible with the presence of an acholuric jaundice; it is, moreover, well known that this disorder may be clinically silent for long periods of time. In the case (2) the extensive destruction of bone marrow throughout the body is to be remembered. In case (4) the cause of death was a prepyloric carcinoma but whilst it is entirely possible that this disease may account for the severe anaemia attention should be called to the remarkable appearance of the spleen: its enlargement, its density, its histological appearance and the enormous amount of haemosiderotic pigment is entirely compatible with the presence of an acholuric jaundice and the same goes for the haemosiderosis of the hyperplastic bone marrow. That a carcinoma of the stomach may develop also in an individual with haemolytic jaundice is of course by no means remarkable, but the features just mentioned tend to further the conclusion that the anaemia in the case (4) had been of long duration. No details are to be obtained about the cases (7) and (8), except the information that it dealt with anaemia. The material may accordingly be summarized thus. A severe anaemia was present in all cases examined in this regard. The cause of the anaemia was in cases (3), (5), (6) and my own case acholuric jaundice, in case (2) destruction of the bone marrow proper by osteitis fibrosa, in case (4) carcinoma of the stomach, probably also acholuric jaundice, in cases (1), (7), and (8) not recorded, although the possibility of acholuric jaundice obviously is to be considered also here. Considering the evidence hence available it seems entirely reasonable to look upon the formation of the heterotopic bone marrow masses as a compensatory phenomenon, as an

filled with gall stones. Pituitary adenoma. Bone marrow apparently not examined. On each side of the thorax at the fifth rib near the vertebral column a small, reddish, smooth, encapsulated mass (diameter 2.5 cm) adherent to the ribs with fibrous tissue. Microscopy of these masses: slightly hyperplastic normal bone marrow structure; iron stain positive (Prussian blue reaction).

2. SALEEBY (1925): Coloured female, aged 21. Antemortem report in 1922 by YOUNG and COOPERMAN. Osteitis fibrosa cystica generalisata Engel-Recklinghausen. Necropsy performed by SALEEBY: »In the thoracic cavity arising from the parietal pleura a large rounded mass, reddish and measuring about 6 cm in diameter was noted. Though adherent to lung substance with fleshy bands and spicules of bone it had probably arisen from the rib.» Microscopy showed a typical hyperplastic bone marrow structure, containing the various cellular elements of the marrow parenchyma, with the exception of the giant cells which were a predominant feature in the sections of the bone marrow proper.

3. RICH (quoted by BRANNAN 1927): Male individual with acholuric jaundice. Post mortem: kidney-sized tumour masses of bone marrow were found within the thorax. The spleen had been removed some time before death.

4. PLONSKIER (1930): Female, aged 70, died of ulcerating adenocarcinoma of the lesser curvature of the stomach. Marked general anaemia before death. Metastases in the liver and the lymph nodes around v. porta and aorta. Marked hyperplasia and hemosiderosis of the bone marrow. Spleen enlarged (1,300 Gm), extremely hemosiderotic. Paravertebral, subpleural masses, hazel-nut-sized—hen-egg-sized, with no connection to the underlying vertebra; the masses were typical bone marrow, rather much loaded with hemosiderin.

5. LORD DAWSON (1931): Female, aged 53. (Case Labourne.) Acholuric jaundice since girlhood. Severe anaemia. Necropsy: spleen enlarged ($2^1/_2$ lb), cut surface with a rich dark-red pulp, liver enlarged ($5^1/_2$ lb), gall stones, kidneys gave marked reaction for free iron. Bone marrow throughout rich and red, even in the tibia. »Beneath the parietal pleura in the costovertebral angles and of the left side of the sixth to tenth thoracic vertebrae were four nodules of ectopic marrow — — in close contact with bone, and showed a rugged surface when dissected from it.» Histologically the ectopic marrow was strikingly active with numerous mitoses erythroblastic more than leucoblastic.

6. HARTFALL and STEWART (1933): Female, aged 52. Acholuric jaundice, obviously since decades. Considerable anemia. Died from blood transfusion. Hyperplasia of bone marrow. Spleen enlarged — — on section firm, solid, reddish. A large reniform mass of dark maroon colour lay upon the right lateral surface of the 7th to 9th dorsal vertebrae and

the corresponding transverse processes and angles of ribs, a somewhat smaller similar mass was present on the left side opposite the 8th and 9th dorsal vertebral bodies. The parietal pleura was covering these masses which were completely circumscribed without any communication with the marrow of adjacent ribs or vertebrae. On microscopy the heterotopic tumours show the structure of actively erythroblastic bone marrow.

7, 8. HUNTER (quoted 1933 by HARTFALL and STEWART). Two cases of anaemia with massive heterotopia of bone marrow, with the same anatomical location as in the case described by HARTFALL and STEWART.

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endeavour of the body to meet the demands induced by the causing anaemia. This apprehension is substantiated also by the hyperplastic bone marrow proper, which in our own case even was evidenced by the roentgenological appearance of the bone system, notably so the calvaria. It is, finally, a remarkable feature that the majority of the observations concerned females; such was the case in no less than 6 out of 7 patients, where the sex was recorded. Whether any hormonal factors may be responsible for this feature is uncertain, but the importance of the pituitary gland for the development of compensatory renal hypertrophy in connection with nephrectomy, as set forth by WRETE, is a topic to be remembered in this connection. A more mechanical factor which will be discussed below may be found in the different pattern of respiration in males and females.

ad (2). *The formal origin.*

What is the matrix of the heterotopic bone marrow tumour, encountered in the present intrathoracic disorder? When similar growths are about in the retroperitoneal space it seems entirely reasonable to assume that tissues still retaining the embryologic potentialities of hematopoiesis may respond to some stimulus, for example the same which, in anemia, calls forth hyperplasia of the bone marrow. PETRI (1925) showed, in a series of forty adults, suffering chiefly from acute infections, that the majority presented small patches of hematopoietic tissue in the retroperitoneal fat (*cf* the observations on the hematopoietic foci in the fat of the breasts, palms and soles of new-borns, as well as in the broad ligament). These patches may well represent the matrix of several heterotopic bone marrow masses in the pelvis of the kidney, in the retroperitoneal tissue and in the presacral region. As to the bone marrow formation of the adrenals attention may be called to the investigations of VON Soos on the minute cortical fat-cell nests, occasionally to be encountered; these nests are believed to be derived from the reticulum of adrenal cortex, which in several regards is similar to that of the bone marrow (fat-collecting, forming red and white blood cells etc.). With regard, however, to the intrathoracic heterotopic bone narrow, one has to look for another explanation. The following possibilities will apparently have to be considered:

1. The matrix may be derived from patches of hematopoietic tissue, similar to those described by PETRI. This possibility is merely hypothetical since no such patches have ever been observed in the thorax and since it would be difficult to account for the localization in a subpleural, paravertebral region almost devoid of fat whereas no similar tumours ever have been encountered in the fatty tissue of mediastinum proper.

2. The matrix may be represented by the pleura. Since the coelomic lining is able to engineer the formation of the spleen with its haematopoietic abilities this possibility might not seem entirely unreasonable. It may also be remembered that myeloid changes at least once have been observed in the pleura (in the case of WADE, quoted by BRANNAN, where there was anaemia due to a sclerosis of the bone marrow). Yet we do not believe the pleura to be the responsible matrix. The structure of the masses in question is that of bone marrow, not that of spleen and it seems difficult to account for the constant localization, should the pleura be the matrix.

3. The growths may be represented by enlarged lymph nodes. So-called red lymph nodes have been described in anaemic infants, which nodes present a marked hematopoiesis and should be distinguished from the true hemal lymph nodes, where the colour is due to circulating blood in the lymph channels (BRANNAN). However, the lymph nodes are particularly prone to adapt myeloid activities in infants but not in adults, and no lymphoid tissue whatsoever could be distinguished in the growths here under discussion. Moreover, it would be difficult to account for the selectivity of the posterior mediastinal lymph nodes, which would here be about. In case I described by BRANNAN (an infant) all mediastinal lymph nodes were red lymph nodes, as were also several other nodes (the lumbar and inguinal).

4. The heterotopic bone marrow has apparently no connection with the marrow of adjacent bone (ribs, vertebrae). There is, however, some evidence indicating the possibility that the ectopic masses may be formed from branches of the intercostal veins. Firstly, there is not infrequently a certain segmental arrangement, for example in the cases of DAWSON and PLONSKIER. Secondly, formation of blood is generally intimately connected with the vascular system, a fact which may be demonstrated also in heterotopic bone marrow masses as for example in the retroperitoneal tumour operated upon by HOFSTÄTTER and SCHNITZLER, where the blood forming activity was mainly to be found in connection with the vessels, or in case II (a young woman), described by BRANNAN, where heterotopic marrow did develop in the organizing thrombs of the broad ligament veins. It may be added that heterotopic marrow has been observed in the wall of the thoracic portion of the inferior vena cava (BRITES and CUNHA, 1935). Finally, there are the important observations of CONE (1925) about the occurrence of bone marrow in the intercostal veins. It had been known since a long time by the pathologists that bone marrow giant cells sometimes may be encountered in the lung capillaries (ASCHOFF and others) and even whole marrow has been found as emboli in these capillaries (MAXIMOW). CONE, investigating this subject, found bone marrow filling the intercostal veins in no less than 68 cases out of 250

necropsies. He states that age and sex had no influence, that a passive congestion or dyspnoea aid in the production of the phenomenon and that »it appears that some change in the blood itself is a prerequisite». The marrow in the veins corresponded exactly with the appearance of the marrow in the rib. »The haversian canals are not infrequently seen exposed at cartilage or periosteum. This was first noted in a case of osteitis deformans with chronic passive congestion. It suggested a means by which whole marrow could be found in veins about bone. The more evident cause of this unusual condition is a mechanical one (hydraulic pressure with suction by difficult breathing) in cases in which the marrow has been more or less changed — reverted more or less to the embryonal — and its cells are more active than usual.» CONE does not mention haemolytic jaundice but it is obvious that the hyperplastic bone marrow in this condition will meet the requirements hence stated. The interesting features that the intrathoracic heterotopic marrow masses are likely to be found mainly below the 6th costovertebral segment[1] may perhaps be accounted for by the impairment of the venous circulations in this region by the less adequate diaphragmatic respiration in females. It may be remembered that most of the cases here concerned were females, and that the 6th rib represents the »watershed» between the two pattern of respiration.[2] It is perfectly obvious that if bone marrow is thus available it will be called upon to meet the requirements induced by the haemolysis in acholuric jaundice. Hyperplasia will occur, the result being the tumour-like aggregates here in question. In other words, the primary factor seems to be embolic or metastatic displacement of bone marrow through the intercostal veins, facilitated by the condition of the marrow; the secondary factor will be the compensatory enlargement of the new dominion of bone marrow, induced by the drain of haemolysis. This assumption being granted, it should be emphasized that only a demand of long duration is likely to further the evolution just outlined. It is obvious that acholuric jaundice will be a disorder entirely complying with these requirements.

ad (3). *Clinical conclusions.*

From practical clinical point of view the main conclusion from the present observation seems to be that if a paravertebral intrathoracic »tumour» has been found, the possibility of heterotopic bone marrow has to be considered in the epicrisis, particularly if the patient is a woman with acholuric jaundice. The case here described does also furnish an

[1] PLONSKIER 6th—10th, DAWSON 6th—10th, HARTFALL and STEWART 7th—10th resp. 7th—9th, my own case 7th—9th costo-vertebral segment.

[2] References on this subject to be had in STUMPF-WEBER-WELTZ' Röntgenkymographische Bewegungslehre, Thieme 1936.

illustration to the ability of the bone marrow proper in haemolytic jaundice to encroach upon the bone so as to produce a picture which for the less experienced may resemble neoplastic destructions. If this phenomenon, as in the present case, is connected with an intrathoracic tumour-like shadow, the erroneous conclusion may easily be drawn that a malignant tumour, for example a pulmonary carcinoma, with metastasis is about, a mistake which not only may induce prognostical errors but also delay the adequate treatment.

SUMMARY

The subject of extra-medullary hematopoiesis is reviewed. The following possibilities may be distinguished: hematopoiesis in connection with a) neoplastic conditions (haemangio-endotheliomas, leukemia), b) formation of bone, c) microscopic foci in organs embryologically adapted for hematopoiesis, d) macroscopical masses, mainly in the retroperitoneal space, occasionally in the thoracic cavity.

A case is described where a tumour-like mass of heterotopic bone marrow was encountered in the thorax of a woman, suffering from acholuric jaundice. The true character of the condition was realized more than 4 years before death, this apparently representing the first case where the diagnosis of the intrathoracic growth was established intra vitam. A few similar instances have been observed post mortem and are briefly recollected. Most of them concerned females with hemolytic jaundice.

The massive deposits of heterotopic bone marrow should be considered as a compensatory adjustment to meet the increased demand for red blood cells. With regard to the formal origin of the intrathoracic deposits of bone marrow it is possible that intravenous metastasis of the marrow into the intercostal veins is of importance.

The clinical conclusion seems warranted that if an intrathoracic paravertebral tumour is encountered the possibility of heterotopic bone marrow should be considered, particularly perhaps if the patient is a woman with acholuric jaundice.

ZUSAMMENFASSUNG

Es wird die Frage der extramedullären Hämatopoese besprochen. Es sind folgende Möglichkeiten zu unterscheiden: Hämatopoese im Anschluss an a) neoplastische Gebilde (Hämangio-endotheliome, Leukämie), b) Knochenbildung, c) mikroskopische Herde in Organen, die embryologisch der Hämatopoese dienen, d) makroskopische Massen, vor allem in Retroperitonealraum, hin und wieder aber auch in der Brusthöhle.

Es wird ein Fall beschrieben, wo eine tumorähnliche Anhäufung von heterotopischem Knochenmark in der Brusthöhle einer Frau gefunden wurde, die an acholurischer Gelbsucht litt. Der wahre Charakter des Krankheitszustandes wurde mehr als 4 Jahre vor ihrem Tode festgestellt, und zwar ist dies offenbar der erste Fall, wo die Diagnose des intrathorakalen Wachstums intra vitam gestellt wurde. Einige wenige Fälle ähnlicher Art sind post mortem beobachtet worden und werden hier kurz wiedergegeben. Es handelte sich in der Mehrzahl um Frauen mit hämolytischer Gelbsucht.

Die Bildung von massiven Herden von heterotopischem Knochenmark ist als eine Kompensationsmassnahme zur Befriedigung des erhöhten Bedarfs an roten Blutkörperchen anzusehen. Was die formale Herkunft der intrathorakalen Ablagerungen von Knochenmark anbelangt, ist es denkbar, dass intravenöse Metastasen von Mark in die Interkostalvenen von Bedeutung sein können.

Es scheint die klinische Schlussfolgerung berechtigt, dass man, wenn man einen intrathorakalen paravertebralen Tumor findet, an die Möglichkeit von heterotopischem Knochenmark denken muss, vielleicht ganz besonders, wenn es sich um eine Frau mit acholurischer Gelbsucht handelt.

RÉSUMÉ

L'auteur examine l'hématopoïèse extra-médullaire. Il distingue l'hématopoïèse en relation a) avec des processus néoplastiques (hémangio-endothéliome, leucémie), b) avec l'ostéogénie, c) avec des foyers microscopiques dans des organes embryologiquement destinés à l'hématopoïèse, d) avec des masses macroscopiques, principalement dans l'espace rétropéritonéal et, occasionellement, dans la cavité thoracique.

Il décrit le cas d'une masse de moelle osseuse hétérotopique, ayant l'aspect d'une tumeur, trouvée dans le thorax d'une femme souffrant d'ictère acholurique. Le vrai caractère de l'affection ayant été précisé plus de quatre ans avant la mort, on serait en présence du premier cas où le diagnostic de la tumeur intrathoracique ait été posé durant la vie. Quelques cas semblables ont été diagnostiqués *post mortem* et sont brièvement mentionnés. La plupart concernait des malades femmes atteintes d'ictère hémolytique.

Les dépôts massifs hétérotopiques de moelle osseuse devraient être considérés comme une réaction compensatrice d'adaptation nécessaire pour couvrir la demande d'érythrocytes. En ce qui concerne l'origine formelle des dépôts intrathoraciques de moelle osseuse, il est possible que les métastases intra-veineuses de moelle osseuse dans les veines intercostales jouent un certain rôle.

Il semble donc que si l'examen révèle la présence d'une tumeur paravertébrale intrathoracique, la conclusion clinique se justifie de penser à la possibilité d'un foyer hétérotopique de moelle osseuse, particulièrement peut-être s'il s'agit d'une malade atteinte d'ictères acholurique.

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FROM THE RADIUM CENTER, COPENHAGEN (CHIEF: JENS NIELSEN, M. D.)

ADAMANTINOMAS OF THE JAW, WITH REFERENCE ESPECIALLY TO THEIR TREATMENT[1]

by

Karen Lübschitz

Adamantinomas are epithelial tumors occurring chiefly in bones, especially in the jaws. They are usually stated to be rare; nevertheless, H. B. G. ROBINSON could in 1937 collect 379 cases from the literature, and from time to time they will be met with in any surgical service of even moderate size. Though the tumor is benign histologically, it often proves clinically malignant, owing to its particular features. It was first described in 1879, by FALKSON; but already from before that time there are several descriptions of cysts in the jaw which probably have been adamantinomas.

The name adamantinoma appears for the first time about 1900, probably introduced by BORST, and has since been the usual designation for this type of tumor, though also the name ameloblastoma is sometimes seen. Both terms have been formed with a view to expressing the fact that the tumor develops from the amenoblasts.

The most frequent location is in the jaws, most often in the lower. Only in 16.3 per cent of the 379 cases collected by ROBINSON was the tumor in the maxilla. Since 1892 it has been known that it can also occur intracranially, in the vicinity of the infundibulum, developing from non-obliterated remnants of the fetal cranio-pharyngeal duct. The first description of such occurrence was given by ONANOFF; since, the subject has been dealt with by several authors, particularly by CRITCHLEY & IRONSIDE in 1926, FRAZIER & ALPERS in 1931, and in 1934 by OLIVER & SCOTT, who have collected the cases reported in the literature up to then. In 1913, B. FISCHER published the first case of adamantinoma in the tibia. Since then several similar cases have been reported. In 1940, the number was summed up, by HEBBEL, to 15 in all.

In the jaw, at least, adamantinomas are a little more frequent in women than in men. Of the cases in ROBINSON's material. 54.3 per cent were

[1] Submitted for publication, Jan. 22, 1945.

female. The tumor most often develops between the ages of 20 and 40 years, but has been seen to occur both as early as at birth and as late as at the 76th year of age. Its growth is slow, and in the beginning it does not give rise to symptoms; but as it increases in size it causes the bone in which it is situated to expand. This first interferes with chewing; later, deglution and respiration may become difficult, there may be pain and hemorrhages, perhaps spontaneous fracture. Owing to the slow growth it may often be several years, though, before the symptoms become so marked that they cause the patient to consult a physician.

Morphologically, two forms of adamantinoma may be distinguished between: the solid and the polycystic. The former is the rarest; according to ROBINSON it is found only in 19 per cent of cases. ROBINSON and several other authors believe, however, that it is only a question of different stages of development, the tumor being solid to begin with and the cysts a later, gradual development. Both ROBINSON and KRONFELD have been able to demonstrate such a development in one of their cases. The solid adamantinoma is a soft, well defined, smooth tumor with connective-tissue capsule; the polycystic has no such capsule and presents a lobular appearance; only when the tumor is very large all the cysts seem as fused together, so that the tumor becomes smooth.

Histologically, the appearance of the adamantinoma is very characteristic. The solid tumor consists of a branching network of solid epithelial strings composed of cuboid-cylindric cells in a connective-tissue stroma, or the branching epithelial strings may be composed of a network of stellate cells surrounded by a palisade-work arrangement of cylindric cells, perhaps with an intermediate zone of more cuboid, polygonal or oval cells between these two layers. The histologic components of the cystic adamantinoma are the same; but here a cystic transformation has taken place, notably in the layer of stellate cells (stellate reticulum cysts), but also in the connective tissue, though the latter is no doubt of rather slight importance. The development of the cysts is chiefly due to vacuolar degeneration of the epithelial cells, but according to KROMPECHER it may also be the result of absorption of colloid into the latter. Finally, it seems that the cysts may in rare cases be composed of lipoid pseudozanthoma cells. One author, PAPADAMITRIOU, thinks that the fluid may also be formed by secretion from the cells of the enamel pulp.

It is the stellate cells, in connexion with the palisade cells, which make the picture characteristic, histologically. The former, with their central nucleus and long protoplasmic processes, contrast with the palisade-formed layer, which consists of high, cylindric epithelial cells with oval, slightly stainable nuclei lying towards the interior of the cell string, so that there out towards the basal membrane is formed a margin of

protoplasm, which stands out in lighter design because the protoplasm is light, homogeneous or slightly granular. But the picture is not always so typical. Often there will be cuboid or polygonal cells, in one or several layers, or more irregular disposed. Sometimes there may be onion bodies or calcification, but no enamel or dentine. As a rule, there are no atypical nuclei. The connective-tissue stroma is most often fibrillar, poor in cells; but in the solid adamantinomas, with cell strings of cuboid-cylindric cells in small strands, it consists of more immature connective tissue, richer in cells. The cyst is as a rule filled with a viscid, ropy, yellowish fluid, which often contains cholesterol crystals.

The etiologic connexion between the adamantinoma and the enamel organ is shown by the similarity of the microscopic structure. Already FALKSON (1879) concluded that the tumor arose from a supernumerary enamel organ or -germ. In 1885, MALASSEZ showed by examination of serial sections of jaws from fetuses and adult individuals that the enamel organ does not, as until then supposed (MAGITOT), disappear completely during growth, but that there in the adult can be demonstrated small epithelial remnants of it (des débris épithéliaux paradentaires); and he considered these as the starting point from which the adamantinomas develop. All later authors have in the main subscribed to this view, but at the same time it has been maintained by some that an adamantinoma also, as suggested by EVE in 1883, may develop as the result of downward growth of the buccal mucosa; and several others, especially KROMPECHER (1918) and MCGREGOR (1930), have shown that this may indeed be the case. Still, it is also KROMPECHER's belief that the majority of adamantinomas develop from the aforesaid epithelial remnants. He further points out that these tumors are nearly related to the basaliomas inasmuch as both are composed of indifferent cells, with the basal cells arranged as radially disposed cylindric cells. Also the frequent occurrence of onion bodies and the formation of cysts are points in common; and clinically the resemblance shows itself in the slow growth and the often young age of the patients.

To this, ROBINSON objects that the resemblances on which KROMPECHER bases his view are accidental, and that there are also essential differences between the two forms of tumor. Thus, the adamantinomas degenerate cystically, penetrate deeply into bone and most often occur in the lower jaw, rarely — or not at all — in the face or neck. The base-cell carcinomas, on the other hand, have a tendency to ulcerate, remain superficial, and are rarely, if ever, seen in the lower jaw, while they are of common occurrence in the face, in the skin of the cranium in general, and in the neck.

In 1913, HESSE called attention to the difference between the adamantinomas that show the typical structure of stellate cells surrounded

by a palisade-arrangement of cylindric cells, and those composed of less regularly disposed, more uncharacteristic cuboid or oval cells; and he suggested that the former were derived from cells from the inner epithelial layer of the enamel organ, the latter from the outer; corresponding to the different appearance of the cells of the two layers. KRONFELD has, however, in 1930, given an other explanation of the same phenomenon. He thinks that the adamantinomas presenting the typical microscopic picture arise from cells from a later stage of the dental development than the histologically less typical ones; because the same difference is found between the early stage of that development, when there are only dental laminae with a few layers of cuboid cells, and the later stages, in which the enamel organ contains both cylindric and stellate cells.

The adamantinomas do not contain enamel. It is true that CHIBRET (1894) reports a case in which it was found and mentions a similar observation by BERNAYS (1885), but none of the later investigators has been able to demonstrate enamel in the adamantinomas. As several authors (E. SCHMIDT, KRONFELD, ROBINSON) point out, this is because the formation of enamel is conditioned by the presence of dentine, such as it is seen in the development of the normal teeth, where the ameloblasts do not begin to form enamel until the odontoblasts have formed the ivory. Since the adamantinomas do not contain odontoblasts, there cannot be any formation of enamel, either. A different thing is that sometimes a tooth may be found in the tumor, in some cases corresponding to a hiatus in the denture, but oftener to a supernumerary tooth; but this only means that the adamantinoma has developed from the epithelial remnants in the vicinity of the tooth in question.

As contributory cause of the formation of adamantinomas, several authors, among them ROBINSON (and, according to him, NEW) and JACOBS (1939), mention irritation, especially in the form of difficult dentition. They find support for this in the fact that adamantinomas in the neighborhood of the third molar, where these tumors are most frequent, generally occur about the thirty-third year of life, and in the neighborhood of the canine about the twelfth to thirteenth year, corresponding to the eruption of these teeth.

Adamantinomas are, as a rule, benign neoplasms, inasmuch as their growth is expansive and not destructive. Sometimes there may be a moderate degree of infiltration in the margin, but there is no considerable invasion of the adjacent organs, and metastases are no part of the typical picture. Malignant adamantinomas exist, though; and MC GREGOR has, in 1935 collected and critically analysed 27 such cases from the literature. In some of the cases it was the stroma that had become sarcomatously transformed, but in others it was the adamantinomatous

tissue itself which showed its malignancy, for instance by metastasising. This last was the case in 10 patients. On the whole, these malignant cases are rare, however. As a rule, the adamantinoma is, histologically, a benign tumor. Nevertheless it may in its slow growth, from a beginning without symptoms, develop into becoming a year-long torment to the patient, recurring despite repeated surgical intervention, and perhaps, though still histologically benign, eventually determining a fatal issue.

Though the question of the therapy is therefore of the greatest importance, it has, on the whole, been little discussed by the various authors. Both surgical treatment and radiation therapy are mentioned; the former, as the oldest, being also the one mostly employed. Both roentgen- and radium treatment have been tried in several places, though; as seen, for instance, from a case-material from Stockholm presented by Mc Gregor in 1935, and from several reports of cases, for instance by Feinbrunn (1930). In one of McGregor's cases, the tumor disappeared completely under teleradium treatment, but this result was unique; in all the other cases mentioned, radiation treatment proved without effect. It also seems that this therapy has been more or less abandoned everywhere.

Operative removal of the tumor has been practiced ever since its nature was recognised, and also before that time. Both enucleation, cauterisation and resection of the portion of bone containing it are mentioned in the literature. The clearest and most precise statements respecting the indications for the different forms of surgical intervention are given by Robinson (1939). He points out that whereas enucleation and cauterisation are sufficient to remove the adamantinoma while it is still in the solid stage, effective removal of the tumor after it has undergone cystic transformation can only be accomplished by resection of the entire portion of bone involved, because cell strings during the expansion of the tumor in the course of this transformation are forced into the bony tissue. According to Robinson it appears that Ivy & Curtis even recommend primary resection, — probably because they reason that the surgeon seldom sees the adamantinoma in its first stage.

Author's Material

In order to illustrate the difficulties which the treatment of these tumors presents, and to fasten the picture of the course of the disease, I shall in the following review the material of adamantinoma cases from the Radium Center in Copenhagen, from the years 1932—1943. The material comprises 11 cases, 7 male and 4 female. Three of the patients were under 20 years old (the youngest 8 years old), three between 40 and 50, five over 50 (one of these 75 years old). The duration of the affec-

tion prior to the time when the patients sought medical advice was in most of the cases remarkably short, in nine of them only a few months. Only in two cases had the patient been going with the tumor 5—6 years before he consulted a physician.

The diagnosis was in most of the cases established at once by roentgen examination and biopsy; only in two cases did respectively 6 and 9 months pass before the necessary examinations were made which revealed the nature of the affection. In nearly all the cases, the symptom which brought the patient to a doctor was a swelling at the site of the tumor; only in one case was there an ulceration of the gum, and only one patient was troubled with pain and nasal stegnosis; but in his case the affection was also six years old.

In 7 cases, the tumor was situated in the upper jaw, in 4 in the lower. This distribution, which is very different from the one usually found, is probably due to the small numerical size of the material. On the other hand, it accords with what in the literature is stated to be the usual; namely that the tumor usually is situated in the molar region. Only in the cases where it has reached a considerable extent already at the first examination, may it be difficult to determine exactly whence it has arisen. A remaining tooth in connexion with the tumor was only found in 3 of the cases.

The roentgen examination is, of course, an important aid to the diagnosis; especially in the lower jaw it may often with considerable certainty be established on the basis of the roentgenologic picture. In the film the tumor shows in this bone as a well defined rarefaction, or as several more or less confluent rarefactions, which often cause expansion of the bone. In the upper jaw the picture is less characteristic. There, the tumor often, at least in the beginnning, shows itself only by a blurring of the maxillary sinus, sometimes by an expansion of the latter; and only after some time do also signs of destruction of the bone appear. But in any case only the histologic examination, — after biopsy or operation, — makes the diagnosis absolutely sure.

All the cases in my material were verified by microscopy, which showed typical picture of adamantinoma. In 8 of them there was a more or less differentiated connective-tissue stroma containing strings or groups of epithelial cells, in the center polygonic or stellate, in the periphery palisade-formed, with oval nuclei. In 5 of these eight cases, the tumor was cystic, which could also be seen at the microscopy; in the 3 others it was solid. The solid form was thus markedly well represented in the material. The patients in whom they were found were the youngest of the eleven, respectively 8, 12 and 17 years old, and thus confirm KRONFELD's observation that solid adamantinomas occur oftener in young subjects than in older.

Fig. 1.

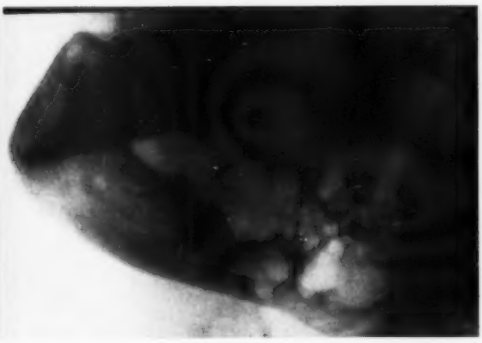

Fig. 2.

Fig. 1. Small polycystic adamantinoma in the lower jaw of a woman aged 66 years. Duration, 1 year.

Fig. 2. Same patient as Fig. 1, ten years later.

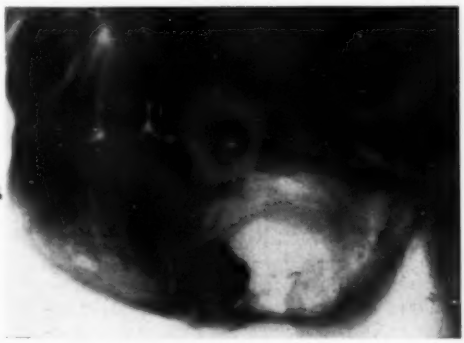

Fig. 3.

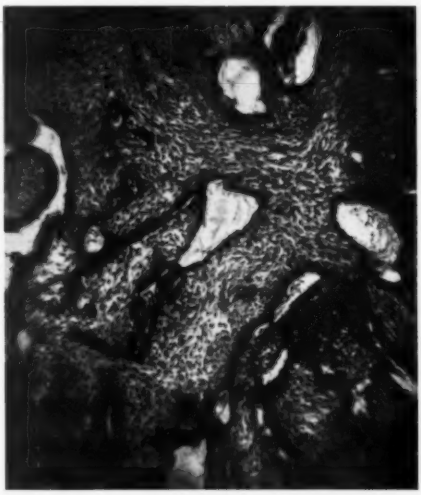

Fig. 4.

Fig. 3. Solid adamantinoma in the lower jaw of a boy 12 years old. Duration, 2—3 months.

Fig. 4. Solid adamantinoma. Broad, compact strings of epithelial cells, consisting of stellate cells, separated from the scanty stroma by a palisade-arrangement of cylindric cells. (Magnification ×35).

Fig. 5.

Fig. 6.

Fig. 5. Polycystic adamantinoma. Between the epithelial cells there are numerous cavities, and only adjoining these and the stroma are there cylindric cells disposed in palisade order. (Magnification ×35).

Fig. 6. Atypical adamantinoma. Irregular heaps of rather undifferentiated epithelial cells, with only here and there incipient palisade arrangement. Great resemblance to »Krompecher's carcinoma». (Magnification ×35).

Three cases, in which the microscopy of the tumor showed an atypical picture, must be described a little more fully.

Case I. — Man, 44 years old, (Case record no. 12036), who for 5—10 years had had a tumor in the right side of the hard palate. In 1932 he had been given roentgen treatment (about 120 skin-erythema doses directly on the tumor, through open mouth; distance, 30 cm.; filter, 0.5 mm. Cu. + 0.5 mm. Al.) without effect. Referred to the Radium Center Feb. 15th, 1935. The tumor at that time about 5—6 + 3—4 cm. large, situated in the right side of the hard palate, covered with mucous membrane, firm in some places, softer in others, not displaceable. Roentgen examination disclosed nothing abnormal. Operation advised, but refused by patient. During the next years slow progression, and in 1938 increasing pain, whereupon operation was consented to. On May 18th, same year, removal of the tumor by enucleation, which was only partly successful, however.

Microscopy (FRIDTJOF BANG): The greater part of the tumor tissue consists of large heaps of hardly differentiated, epithelial-like cells with round or oval nuclei set close together and surrounded by cytoplasm, without cell membrane; or of cell heaps in which the cells are more differentiated, especially in the periphery of the lobular heaps, where they in many places show distinct cylindric shape and palisade arrangement. The same

is the case with the cells that form the limits of the small, round or cleft-like cavities seen in many of the heaps. In some places, especially in the heaps where the cells are only little differentiated, there are hyaline deposits such as seen in cylindromas. In some places there is a clear demarcation between the lobular formations and the connective tissue, in others there is a diffusely infiltrating invasion into the latter; this is particularly the case in a small portion of the tumor tissue consisting of hyaline connective tissue poor in cells, with scattered groups of epithelial cells in the peripheral part. There are no absolutely typical adamantinomatous areas anywhere, but, as said, the cells have a distinct tendency to differentiation into cylindric, sometimes high and clear cells. *Diagnosis*: Atypical adamantinoma.

A year later, the tumor recurred, grew slowly and caused neuralgiform pains. On Nov. 7th, 1940, it was therefore excochleated with electrocoagulation knife, and the patient has since been free from symptoms for three and a half years.

Case II. — Man, 46 years old, (Case record no. 18123), who for about a year had had a slowly growing swelling corresponding to the left side of the palate. No pain, but a feeling of tenderness when masticating. In March, 1938, roentgen-examined at the hospital in Stubbekobing, and a rarefaction found in the bone around a retained oot of a tooth, whereupon an operation was done, at which the tissue was found to be very friable. Microscopy of biopsy sample resulted in the diagnosis of adamantinoma, and on May 4th, same year, the patient was referred to the Radium Center. Here a considerable, firm swelling of the entire left side of the hard palate was found, extending across the midline to the right alveolar process. Roentgen examination showed blurring of the left maxillary sinus and a defect in the bone in the posterior part of the molar region. *Roentgenologic diagnosis:* Tumor of the left upper jaw. On May 16th the tumor was extirpated with electrocoagulation knife and enucleated, whereby the greater part of it was successfully removed. The hard palate was found to be perforated.

Microscopy (Fridtjof Bang): The tumor is of partly organoid structure and consists of islands and lobes of only slightly differentiated, epithelial-like cells, between which there are numerous cavities, which seem to be full of secretion. In some places, these cells invade the connective tissue, where they form narrow streaks between the fibrils. There is no palisade-arrangement of cells, or anything else which makes it possible to establish the diagnosis of adamantinoma with certainty; if it is one, it must be a very atypical form. The tumor tissue very much resembles that of a basal-cell carcinoma with secretion between the cells (the type which Vasson calls: adamantoid). Diagnosis: ? adamantinoma. (Four later microscopies, in 1938—1939, showed precisely the same histologic picture.)

The tumor soon recurred, and was painful; so on Jan. 4th, 1939, renewed extirpation with electrocoagulation knife had to be done, and the operation repeated on the 16th, though on both occasions the growth had to all appearances been removed entirely. But still it recurred again, causing pain, and now also nasal stegnosis. From Jan. 16th to 31st, roentgen was given, palliatively, to 3 fields: 1110+910+1125 r, in doses of 100—125 r (180 kv., 4—6 ma., distance 50 cm., Thoraeus filter), and again Feb. 5th to 19th, to 4 fields: 1250+900+900+600 r, under the same conditions as before, except that the filter was 0.5 mm. Cu. Finally, a third treatment was given, from May 15th to June 6th, 1940, to 2 fields: 1700+1000 r, and from Jan. 27th to Feb. 6th, 1941, a fourth, to 4 fields: 250 r to each, through Thoraeus filter. In spite of all this, the tumor persisted unchanged; the only effect of the treatments was some temporary relief from the pain. Until as late as in 1940 it was thought that the tumor might perhaps be completely removed by bilateral maxillary resection, but the patient refused operation. Toward the end of 1941 he died, 4 years after the onset of the disease.

Case III. — Man, 75 years old, (Case record no. 20458), who for 6 months had been aware of an increasing swelling in the left side of his palate. Roentgen examination showed blurring of the left maxillary sinus and destruction of the surrounding bone.

Microscopy of biopsy specimen (FRIDTJOF BANG): The tumor tissue consists of a stroma, rather poor in cells and in some places, about the islands of epithelial cells which it contains, of rather specific appearance, poor in nuclei, staining blue with hematoxylin and with very narrow nuclei. In this stroma there are scattered, irregular groups of small, epithelial-like cells, in many places resembling Krompecher's carcinoma, but in others in process of differentiation, the cytoplasm becoming clear and the cells in the periphery beginning to get palisade form. In the center of some of the cell groups there are cavities, seemingly filled with secretion; and some of these cavities are lined with high, narrow, rather regular cylindric cells. From the whole appearance of the tumor, as well as from its site, there is hardly any doubt that it is an atypical adamantinoma of invasive growth. *Diagnosis:* Adamantinoma.

As effective operative treatment was out of the question, roentgen was given as a palliative. It helped somewhat on the pain, but had no effect on the tumor, which continued to spread, for instance to the orbit, and also showed sign of involving different nerves. The patient died in his home barely three and a half years after the onset of the disease.

Though the histologic picture in these three cases was not quite typical, we have nevertheless at the Radium Center felt it justifiable to consider them as adamantinomas, and there is nothing either in their clinical picture or in their course which speaks against interpreting them as such.

Our treatment of the disease has been partly surgical, partly roentgenologic. Of surgical treatment, four forms were employed: (1) extirpation of the tumor, (2) excochleation of tumor tissue, (3) electrocoagulation of the tumor, (4) resection of the portion of bone where the tumor was situated.

Of extirpation of the tumor there may be question where the growth is so well circumscribed that it can be removed entire. In our material, this condition was only fully present in one case, in a girl 8 years old, with a solid adamantinoma in the upper jaw. The tumor was easily removed, and the postoperative course, with freedom from recurrences five years after the operation, shows that this treatment is sufficient. The same procedure was attempted in two other cases, where the tumor was likewise situated in the upper jaw; but in both it proved to be less well circumscribed than had been supposed, and could not be removed entirely; as subsequent recurrences also confirmed.

Excochleation of tumor tissue and electrocoagulation of the tumor may be considered as the same type of operation, in so far as by either of them the tumor is removed bit by bit; only that electrocoagulation has the advantage that it closes the vessels as the operation proceeds, so that there is less hemorrhage. For that matter, it should be possible to remove the tumor entirely by this method, and, in fact, there are examp-

les of it having been done; but experience shows that it is difficult, and this is also proved by the cases treated in this way at the Radium Center. Excochleation was used in 3 cases, electrocoagulation 4 times, and only in two instances could the tumor be removed so completely that there was no recurrence. In one of these the growth was a solid adamantinoma, the size of a green walnut, in the lower jaw of a boy, 12 years old, who had first noticed the swelling three months before. It had been tried twice before, in another hospital, to scrape it out, but the operations had not succeeded in removing it completely. Since the operation at the Radium Center, the patient has been well and without signs of recurrence for 6 years. The other case was one of those mentioned above, in which the tumor (in the upper jaw) had recurred after an unsuccessful attempt at extirpation. Excochleation two years later resulted in its complete removal, so that the patient has now been without symptoms for 3 years. Of the other five operations, 3 were electrocoagulations performed successively on a patient whose tumor, in the upper jaw, it had already previously been tried to extirpate; but none of the operations succeeded in eradicating the neoplasm completely. In another case, an adamantinoma of the lower jaw, excochleation was performed only once at the Radium Center, but the patient had previously undergone four similar operations elsewhere, in the thirty-six years that the tumor had existed. How great sufferings such a benign tumor may cause the patient is shown by the case histories of these two patients. One of them has already been given (Case II); the other is briefly as follows.

A woman (Case record no. 14911) noticed in 1902, when she was about 30 years old, a tumor in her right lower jaw. She was operated upon, with excochleation of cystic tumor tissue; and later underwent three more operations of the same character (1919, 1925 and 1928), but the tumor continued to recur. Microscopy showed it to be an adamantinoma. Besides, she was in 1933, 1934 and 1935 given 3 series of roentgen treatments, each time 1600—1700 r, in all, by fractioned treatment. In 1928 and 1935 there were fractures of the jaw, which healed again, however. In 1936 she was referred to the Radium Center. There was then a tumor, the size of a small apple, in the right lower jaw, from the angle to the first molar, and roentgen examination showed a corresponding defect in the bone. She had a feeling of constant tension at the site. In 1936 to 1937, she was given 3 series of roentgen treatment, 900—1000 r, in all, each time, with fractured irradiation (180 kv., 40 ma., 0.5 mm. Cu.+ 0.5 mm. Al.), which at least had the effect of bringing some subjective relief. In 1938, excochleation of the tumor; but within a year it recurred again, and in 1939 she was therefore once more given palliative roentgen treatment as before. Since then she has not been treated. The tumor continues slowly to grow, and infiltrates the skin above it. There is a formation of fistulae, but no lymph glands.

It will be seen from this that there is great need of a surgical intervention which will relieve the patients of their tumor more effectively than those already mentioned. As such, there will then be question of (4) resection of the part of the bone containing the growth. This opera-

tion has at the Radium Center been performed in 4 of these cases. In one, the patient was a woman, 44 years old, who had had a cystic adamantinoma in her lower jaw for 19 years. She had been operated on twice previously (probably excochleations), but each time the growth had recurred. The involved half of the jaw was now resected, and the patient has since been free from symptoms for 4 years. In another case, the patient was a young man, 17 years old, with a solid adamantinoma in the upper jaw, which caused destruction of the lateral and inferior walls of the maxillary sinus. A portion of the jaw was therefore resected. The operation was performed only a year ago, but there has been no recurrence since. A third case was that of a cystic adamantinoma in the upper jaw of a man aged 57 years. The tumor was removed 4 years after the first symptoms had set in, and there had been no recurrence when the patient died, nine months later, of an intercurrent disease. The fourth case was judged inoperable already at first sight. The patient had been going with symptoms of a tumor in the upper jaw for six years before he finally consulted a physician. Roentgen treatment was tried, and also diathermy, to relieve the pain; but as the tumor continued to grow and the patient suffered intensely, both maxillae were resected. The involvement was so great, however, that nothing more than a palliative effect could be expected; and, in fact, recurrence set in about a year afterwards, and he died in cachexia.

Roentgen treatment was employed in 5 cases, as a rule *solaminis causa* where no other therapy was possible. Up to 5 series of treatments were given in each case. The dosage varied somewhat. In most cases, about 600 to 1000 r were given to each of 3—4 fields, in a few cases up to as much as 2000 to 3000 r; all fractioned, with single doses of 50 to 150 r; distance, 40—70 cm.; 180 kv.; 4—6 ma.; filter, 0.5 mm. Cu. or Thoraeus. No sure effect was observed on the tumor, but most of the patients experienced some temporary relief from pain as result of the irradiation.

Of the 11 patients composing the material, 6 are at present writing alive, five of them free from symptoms for respectively 6, 5, 4, 3 and 1 years after operation, while one still has a tumor, of 42 years' duration, in the lower jaw. Of the remaining 5, two have died of intercurrent diseases, one of them free from recurrence nine months after the operation, the other with a slowly growing, but otherwise not subjectively troubling adamantinoma of the lower jaw. Two others died of their tumor (in the upper jaw) respectively 10 and about 4 years after they had noticed the first symptoms, and the fifth, at the age of seventy-eight years, after having had the tumor (in the upper jaw) for $3^1/_2$ years; but it does not appear with certainty whether this or some other disease was the cause of his death.

The fact that only 6 of the 11 patients were cured of their adamantinoma, and that the tumor in 2, perhaps 3, of the remaining 5 cases was the direct cause of death, warrants us in speaking of these neoplasms as clinically malignant, even though the growth in all the cases proved to be benign histologically and in none of them metastasised. In two of the cases there was invasion of the surroundings, though; with perforation to the cheek or the nose after destruction of the hard palate; but not until the tumor had been present for several years. It is hardly accidental, either, that the two, perhaps three, cases in which the patient's death was directly due to the tumor, were cases in which the latter was situated in the upper jaw; for in this site there is the possibility that a tumor, perhaps destroying the surroundings in its growth, may compromise the upper air passages, the contents of the orbit and even the base of the brain; whereas tumors in the lower jaw give much less trouble and for many years remain confined to the mandible, even if they cause the latter to expand and thus are apt to some extent to make the intake of food difficult.

These eleven cases thus emphasise the importance of the right treatment being instituted at the earliest possible time. That it must be surgical, is clear. The effect of radiation therapy is so slight that there can only be question of using it as palliative measure in far advanced cases, and even thus it gives only passing and mediocre results. Of surgical methods, it will be of importance to chose the most efficacious, that is to say the one by which the tumor can be removed completely. If the tumor is well circumscribed, which will be the case with most of the solid ones, and perhaps also with cystic adamantinomas in the early stages, enucleation will be the best procedure. If the growth is found not to be so encapsulated that it can easily be removed entire, it will be tempting to proceed to excochleation of the tumor tissue; and it will no doubt also be defensible to try to obtain a good result by this means, though it, as we have seen, in many cases, even if the operation is done most thoroughly, will be impossible to remove outgrowths of the tumor, which sends projections into the canaliculi of the bones, from which then recurrences develop. If excochleation is attempted, the patient should be kept under observation for a considerable period afterwards, and if signs of recurrence appear it should no doubt be decided to resect the portion of bone which is the seat of the tumor. In many cases it will undoubtedly also in the long run be in the patient's best interest to proceed to this operation at once, because it will spare him much suffering later; especially in the case of cystic adamantinomas of any considerable size. The histologic diagnosis of a biopsy specimen may to some extent be useful as a pointer to the best form of operation, because with a solid adamantinoma there will most often be a possibility of its removal by enucleation,

whereas with a cystic the possibility of resection should be considered at once.

SUMMARY

After reviewing the history, location, morphologic and histologic appearance of the adamantinoma, as well as the etiologic relationship between this tumor and the enamel organ, and the therapy, the author gives an account of 11 cases of the disease treated at the Radium Center in Copenhagen during the period 1932 to 1943. 7 of the patients were men, 4 women. In 7 cases, the tumor was situated in the upper jaw, in 4 in the lower. 8 of the tumors were cystic, 3 solid, the latter occurred in the three youngest of the patients. The treatment was partly surgical (extirpation, excochleation, electrocoagulation, resection), partly roentgenologic. The author discusses the results and stresses the clinical malignancy of the tumors, as contrasted to their histologic benignity. She points out that this malignancy makes complete primary removal important; in the case of solid adamantinomas by enucleation, in the case of cystic as a rule by resection. Roentgen treatment can only be used as palliative measure.

ZUSAMMENFASSUNG

Nach einer Übersicht der Geschichte, der Lokalisation, des morphologischen und histologischen Bildes des Adamantinoms, sowie der ätiologischen Verwandschaft dieses Tumors mit dem Emailorgan und der Therapie, berichtet die Verf. über 11 Fälle dieser Krankheit, die in der Zeitspanne 1932—1943 in der Radiumzentrale in Kopenhagen behandelt wurden. 7 der Kranken waren Männer, 4 Frauen. In 7 Fällen sass der Tumor im Oberkiefer, in 4 Fällen im Unterkiefer. 8 der Tumoren waren zystisch, 3 solide, und zwar kamen letztere bei den drei jüngsten Patienten vor. Die Behandlung war teils chirurgisch (Exstirpation, Ausschälung, Elektrokoagulation, Resektion), teils röntgenologisch. Die Verf. bespricht die Ergebnisse und betont die klinische Malignität der Tumoren, im Gegensatz zu ihrer histologischen Gutartigkeit. Sie macht darauf aufmerksam, dass diese Malignität vollständige primäre Entfernung notwendig macht, bei soliden Adamantinomen durch Ausschälung, bei zystischen in der Regel durch Resektion. Röntgenbehandlung kann nur als palliative Massnahme Verwendung finden.

RÉSUMÉ

Après avoir fait l'historique et résumé la localisation, l'aspect morphologique et la structure histologique des adamantinomes, ainsi que les relations étiologiques de cette espèce de tumeur avec l'émail et enfin la thérapeutique, l'auteur rend compte de 11 cas de la maladie traités au Centre de Radium à Copenhague de 1932 à 1943: 7 malades hommes et 4 femmes. Dans 7 cas la tumeur était localisée au maxillaire supérieur et dans 4 au maxillaire inférieur. 8 tumeurs étaient kystiques et 3 solides, toutes trois chez les malades les plus jeunes. Le traitement a été en partie chirurgical (extirpation, excochléation, électro-coagulation, résection), en partie radiologique. L'auteur discute les résultats et souligne le caractère clinique de malignité des tumeurs, malgré leur benignité histologique. Elle souligne que cette malignité clinique impose l'éloignement primaire total de la tumeur, dans les cas d'adamantinome solide par énucléation, dans les cas d'adamantinome kystique généralement par résection. Le traitement aux rayons de roentgen ne peut servir que de mesure palliative.

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AUS DER HEILANSTALT VON MITTELFINNLAND (LEITENDER ARZT: DR. MED. NIILO MÄKINEN)

EIN FALL VON THORAXDEFORMITÄT, DER ALS FOLGE ANGEBORENER MISSBILDUNG DER BRUSTWIRBELSÄULE AUFGEFASST WIRD[1]

von

Risto Elo

Im Thorakalskelett kommen ziemlich häufig Deformitäten vor, die entweder die Rippen oder die Wirbelsäule betreffen obwohl man auch Fällen begegnet, in denen beide zugleich Störungen aufweisen.

In seiner auf einem umfassenden Schrifttum basierenden Arbeit bespricht BOEHM die Rippenstörungen, indem er sie in die Halsrippen und die Missbildungen der eigentlichen Rippen einteilt. Die letzten können nach ihm auf dem Fehlen der ersten Rippe oder deren Verkümmerung, auf interkostalen Scheinwirbeln, ihrer Verschmelzung (KIENBÖCK: Serbsche Anomalie) beruhen. Ausserdem führt BOEHM grössere Deformitäten im Bereich der Thorax an. Dazu gehörten der Scapulahochstand, mit dem überdies Formveränderungen des Schulterblattes, ungewöhnliche Krümmerungen der Wirbelsäule und Defekte derselben, Missbildungen des Schädels, des Gesichtes und der Extremitäten verknüpft sind. Desgleichen sind die Anomalien des Willet-Walscham-Boehm Typus mit angeborener Skoliose, Defekten oder Verschmelzungen der Rippen sowie Schulterblatt-Wirbelsäulen-Knochenbrücken zu den Missbildungen zu rechnen, bei denen eine Deformität der Wirbelsäule besteht. Die Fälle von Fissura-thoracis lateralis und von Grubenbrust gehören ebenfalls zu den grossen Missbildungen des Brustkorbes.

SCHMORL behandelt in seiner ausführlichen Darstellung die Deformitäten der Rückenwirbel. Bei diesen unterscheidet er die Verschmelzung bzw. die Verwachsung der Wirbel miteinander. Auf die erste Weise kann ein einheitlicher Blockwirbel entstehen, bei dem röntgenologisch oft kein Zwischenknorpel zu sehen ist, obgleich es histologisch festgestellt werden kann. Als wichtige Wirbelstörung beschreibt SCHMORL die von der vertikalen Teilung der Wirbel herrührende Deformitäten. Diese Spaltung würde sich aus dem entwicklungsgeschichtlichen Perichordal-

[1] Bei der Red. am 13. III. 1945 eingegangen.

septum im Embryonalstadium erklären. (PUTTI u. a. m.) Nach ihm und ALEXANDER finden sich im Wirbel oft 2 Verknöcherungszentra, während laut KEIBEL und MALL ihrer nur eines vorhanden ist. SCHMORL hat beobachtet, dass in den Fällen mit 2 Verknöcherungszentra, einem rechten und einem linken, eines von diesen weniger entwickelt ist und Skoliose in der Wirbelsäule hervorruft, wodurch eine Thoraxdeformität nebst Rippenstörungen verursacht werden kann. (Abb. 1.)

Ausser den zahlreichen von BOEHM und SCHMORL erwähnten Forschern seien folgende genannt. WALTHER und JONES teilten Rippendeformitäten mit, welche bei der Röntgenuntersuchung Verschattungen hervorriefen, die an die Höhlenschatten von Lungen erinnerten. HARPOTH schildert einen Fall, in dem die interkostale Knochenbrücke röntgenologisch erst während des von einer Lungenblutung verursachten Lungenkollapses hervortrat. RABIN teilt die Rippendeformitäten in Halsrippen, verzweigte, fehlende und überzählige Rippen sowie in solche, die sich auf ungewöhnliche Weise an der Wirbelsäule anhaften. WESSLER und JACHES geben einem Fall wieder, in dem rechts die 3. und 4. Rippe fehlten, ohne dass Pat. Schaden davon hatte. Nach GAGE verursacht ein Defekt von 6—10 Rippen Beschwerden; ebenso das Fehlen aller Rippen (VROLIK). AHLFELD teilt einen Fall von Fissura thoracis lateralis bei gleichzeitigem Lungenbruch mit. LECAPLAIN beschreibt einen vomgenital missgebildeten Thorax, der von vorne nach hinten abgeplattet war, nebst eingehender Grubenbrust, Skoliose, rechtsständigem Herz und Relaxatio diafragmatica. Nach SIMON kommen bei Kindern Rippendeformitäten zu 2.7 % vor und ihre Form erinnert an die bei den Erwachsenen.

Was die Ätiologie derartiger Missbildungen anbelangt, stimmen die Forscher darin überein, dass die primäre Ursache der Störungen in Entwicklungshemmungen während der ersten Zeiten der Embryonalperiode (BOEHM, SCHLANGE, LIEBERKNECHT, SCHEDTLER und BÖTTNER), in fehlerhaften Verhältnissen im Amnion mit Verwachsungen oder abnormen Druck- und Spannungszuständen (BOEHM u. a. m.) zu suchen ist. Nach ERNST darf man jedoch mit vollem Recht annehmen, dass die Ursache der Störung im Embryo an sich liegt. Unter den Missbildungen beobachtet man auch atavistische Erscheinungen (BOEHM). SCHMORL hebt als einen Faktor der Wirbeldeformitäten die Entwicklung der Wirbel hervor. Da sich der Wirbel in der Weise aus dem Urlobus entwickelt, dass aus dem mittleren Teil des Urlobus der Zwischenknorpel der Wirbel wird und der Wirbel selbst sich durch Vereinigung des oberen und unteren Teiles zweier nebeneinanderliegender Urloben bildet, würden zu dieser Zeit entstandene Störungen Deformitäten verursachen. Ausserdem sei noch der oben berührende Einfluss des Perichordalseptums auf die vertikale Teilung des Wirbels erwähnt.

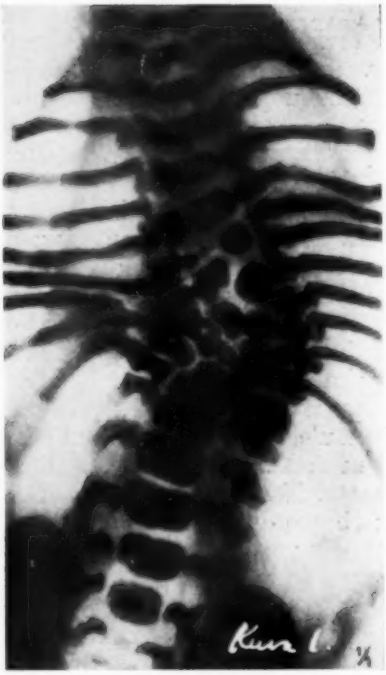

Abb. 1. Die mediane Verteilung der Verknöcherungszentra nach SCHMORL.

Im folgenden berichte ich über eine weit entwickelte Deformität im Thorakalskelett. Den Fall hat mir mein Chef, Dr. med. NIILO MÄKINEN zur Verfügung gestellt, dem ich hiermit meinen ergebensten Dank aussprechen möchte.

A. V. 13-jährige Tochter eines Gemeindearmen.

Anamnese: Hereditas ist bemerkenswert: Mutter schwachsinnig, auch in den vorausgegangenen Generationen schwachsinnige und geistig minderwertige. Die Mutter hat zwei Schwestern, von denen die eine Polydaktilie hat. Die Pat. ist ein 1/1 Kind. Geburtsgewicht 1.7 kg; Entwicklung äusserlich ziemlich langsam, aber in der Schule ist Pat. gut vorwärtsgekommen.

Status praesens: Länge 123 cm., Gewicht 25.5 kg. Pat. steht fest da, wobei sich die rechte Hälfte etwa 4 cm höher als die linke befindet, sie geht und läuft ziemlich schnell umher. Knochengerüst gut entwickelt, keine Zeichen von Rachitis. Zähne ausserordentlich kräftig. Körperbau von mittlerer Stärke. Muskeln bei Extremitäten gleichmässig entwickelt. Kompressionskraft beider Hände gleichstark. Allgemeinzustand ziemlich gut. Atmungs-, Zirkulations- und Verdauungsorgane sowie Nervensystem o. B. Tb. Mikr. Tb. Kulturen —. Pirquet —. WR —. Kahn —. SR 3/6. Blutbild normal. Lungenausk. 0. Lungenröntgen: keine Herdschatten.

Thoraxschatten (Abb. 2 und 3): Rechts ist am Brustkorb der Pat. eine grosse Deformität von der Gestalt eines Defektes festzustellen. Linke Thoraxhälfte stark entwickelt und gebogen. Linke Scapula etwas verschiebbar und hartgelegen. Rechtes Schulterblatt unten in der Vertiefung der Deformität und ihr unterer Winkel bei Haltung der Arme nach abwärts der Wirbelsäule zugewandt. Rechts sind die Muskeln gut entwickelt; links sind die 1:e Oberextremität bewegenden Muskeln wegen der Deformität verkümmert. — Die oberen Rippen scheinen am Brustbein zu endigen, dessen unterer Teil sich plattenförmig nach rechts verbreitet hat und aus dem Processus xiphoideus eine etwa 6—7 cm weit reichende Platte bildet. Hinter dieser kann man in dem Thorax hinein medial von einer 2 Finger breiten Furche palpieren. Den lateralen Rand von dieser bildet eine Knochenplatte die sich nicht an dem Brustbein fixiert. Diese Knochenplatte setzt sich nach hinten oben in der Weise medialwärts fort, dass zwischen ihr und anfangs dem Brustbein, später zwischen den oberen Rippen eine im Anfang etwa 2 Finger breite Furche bleibt, die man nach hinten oben auf die Wirbelsäule zu verfolgen kann, während sich die Furche allmählich verschmälert.

Im Thoraxteil der Wirbelsäule ist eine starke links-konvexe Skoliose sowie eine unbedeutendere kompensatorische rechts konvexe Skoliose in ihrem Lumbal- und Hals-

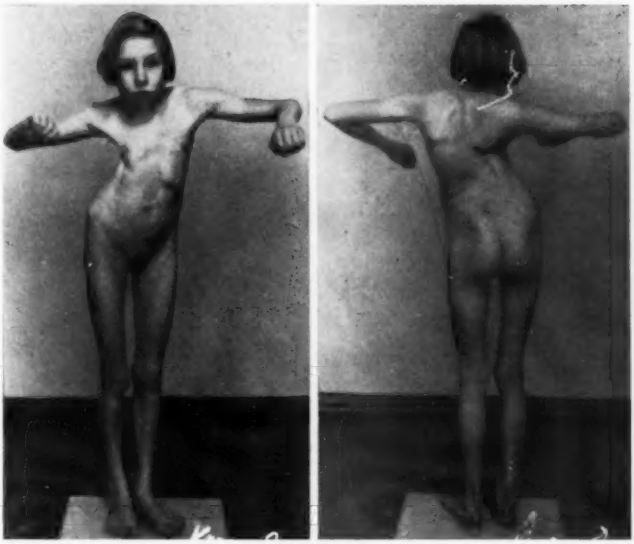

Abb. 2. Abb. 3.

Abb. 2. Die Patientin von vorn mit erhobenen Armen.
Abb. 3. Die Patientin von hinten mit erhobenen Armen.

teil zu bemerken. Die Wirbelsäule weist keine gewöhnliche Lordose oder Kyfose auf. — Bei Beugungen nach vorn ist der Thoraxteil des Rückens ganz unbeweglich, im Beckenteil tritt eine geringe Neigung auf. Bei Beugungen nach der Seite biegt sich der Beckenteil normal, während der Thoraxteil unbeweglich ist.

Röntgengutachten. (Dozent Dr. med. CARL WEGELIUS.)

Columna vertebralis. Thorakalwirbelsäule stark links-konvex skoliotisch mit einer geringfügigeren kompensatorischen rechts-konvexen Lumbal- und ebenso hohen Zervikalskoliose. Die Vert. Th. IV—VIII zu einem grossen »Blockwirbel» verschmolzen, indem rudimentäre Intervertebralräume zwischen Th. IV, V und VI nachzuweisen sind (Abb. 4). In dem Wirbelkörper von Th. VIII findet man eine zweiteilige längsverlaufende offene Spaltbildung, auch der Wirbelkörper von Th. IX ist in gewissem Masse mit einer Zweiteilung versehen. — Der Kalkgehalt und die Knochenstruktur sind in sämtlichen Wirbeln völlig normal, es sind keine Zeichen von entzündlichen Veränderungen (Tub. vertebrae) festzustellen, ebenso keine Zeichen maligner Degeneration. — Die Lumbal- und Zervikalwirbel sind innerhalb des Rahmens der oben angegebenen Skoliose vollkommen normal. Es lenken nur in der Seitenproportion der Lumbalwirbel deren auffallend langgestreckte Wirbelkörper von L II—III die Aufmerksamkeit auf sich, die vielleicht als ein kompensatorischer Versuch aufgefasst werden können, der durch die Thorakalskoliose und die Blockwirbelbildung entstandenen Verkürzung der Gesamtlänge der Wirbelsäule entgegenzuwirken.

Thorax: Die Rippen der rechten Thoraxhälfte sind hochgradig missgebildet und in folgenden Beziehungen verwachsen (Abb. 6). Die Costae I—II und III—IV sind untereinander durch plattenähnliche Bildungen verbunden, deren laterale Enden ihrerseits

Abb. 4.

verwachsen sind. Dieser Konglomerat bildet als Ganzes eine schnabelförmig nach untenvorn verlaufende Platte, die von der Wirbelsäule hinten konkav die rudimentäre rechte Lunge bis etwas vor der Axillarlinie umschliesst, wo sie aufhört und die Lunge unbedeckt von Skeletteilen lässt. — Die unteren Rippen C. V—XII sind bedeutend unvollständiger ausgebildet, C. V—IX sind sehr dünn und untereinander paarweise zu einem ganz schmalen Konglomerat verwachsen, das hinten kaum bis die Axillarlinie reicht. C. X dagegen ist länger und kräftiger und reicht in etwas konkavem Verlauf vor diese Linie. C. XI—XII sind schliesslich wieder schwächer ausgebildet und an ihren lateralen Enden zu einer Platte verwachsen, die sich hinten nur etwas innerhalb der Axillarlinie erstreckt. Zwischen den von C. I—IV einerseits und C. V—XII andererseits gebildeten Konglomeraten findet sich eine von hinten medial abwärts lateral verlaufende Fissura thoracis lateralis-ähnliche Spalte, in der die Lungenbedeckungen ganz skelettfrei sind. In sämtlichen angeführten Rippen lassen weder der Kalkgehalt noch die Knochenstruktur Zeichen entzündlicher oder anderer pathologischer Veränderungen erkennen; Missbildungen dürften als Entwicklungsanomalien aufzufassen sein.

Der linke Teil des Thoraxskelettes ist kompensatorisch stark entwickelt, wie aus den Abbildungen hervorgeht, irgendwelche pathologischen Veränderungen sind nicht darin aufzuweisen.

Scapulae. Die rechte Scapula erscheint an ihrem normalen Platz, sie ist offensichtlich schwächer als normal entwickelt, zeigt aber sonst nichts Pathologisches. Die linke Scapula ist von Form und Grösse normal, liegt aber abnorm hoch und ist in gewissen Massen horizontal über die stark konvexe linke Brusthälfte gestellt. Von der linken Scapula kann mit vollem Recht der Ausdruck »Scapulahochstand» angewandt werden.

Bronchografie. Eine Bronchografie der in Bezug auf ihr Volumen erheblich zusammengedrückten und verkleinerten rechten Lunge zeigt überall normale Füllung des luftführenden Parenchyms der Lunge; Zeichen einer Bronchialstenose sind nicht nachzuweisen.

In meinem Falle hatte die Patientin also eine grosse Deformität der Wirbelsäule nebst einer starken Skoliose und eine davon herrührende Missbildung des Thorax. Auf der rechten Seite des Brustkorbes ist eine Fissura thoracis lateralis zu konstatieren, durch die man in das innere des Thorax medialwärts vortasten kann. Ein eigentliches Lungenbruch ist jedoch nicht vorhanden, was auf der durch die stark links-konvexe Skoliose verursachte Verkrümmerung der rechten Lunge beruht. Auf der linken Seite liegt »Scapulahochstand» vor. Die röntgenologisch festgestellte ungewöhnliche Höhe der Beckenwirbel kann als kompensatorische Zunahme der Länge der Patientin betrachtet werden, obschon die Patientin die durch ihr Lebensalter vorausgesetzte Länge von 146 cm (YLPPÖ) nicht erreicht, wiewohl das Gewicht und die Länge einander gut entsprechen. Als Ursache der Deformität ist meines Erachtens die vertikale Spaltung von Rückenwirbeln mit zwei Verknöcherungszentra anzusehen (SCHMORL), von denen die rechtseitigen schwach entwickelt sind (Th. VIII und IX). Die Ursache dieser Störung scheint mir im Embryo selbst zu liegen (ERNST), zumal wenn man die in der Familie der Patientin auftretende starke geistige und auch körperliche Degeneration in Betracht zieht.

ZUSAMMENFASSUNG

Nach einem Uberblick über die Literatur, die sich mit den Thoraxdeformitäten beschäftigt, teilt Verf. einen schweren, alle Rippen umfassenden Fall von einseitigen Deformität des Brustkorbes und eine gleichzeitige »Blockwirbel»-Bildung in Th. IV—VIII mit. Die Deformität der Lungen betrachtet er als eine sekundäre Folge primärer, angeborener Entwicklungsstörung der Brustwirbel.

SUMMARY

After a survey of the literature concerning deformities of the thorax, the author describes a serious case of one-sided deformity of the thorax comprising all the ribs combined with a grave obstruction in the thoracic vertebrae IV—VIII (»Blockwirbel»). The author is of the opinion that the deformity of the lung is merely a secondary occurrence to the primary congenital disturbance in the development of the thorax.

RÉSUMÉ

Après avoir donné un aperçu sur la littérature traitant des difformités du thorax, l'auteur rapporte un cas grave de difformité unilatérale de la cage thoracique affectant toutes les côtes et l'existence simultanée d'un »bloc vertébral» comprenant les vertèbres thoraciques IV—VIII. Il considère la déformation pulmonaire comme une conséquence d'un vice de développement congénital des vertèbres thoraciques.

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FROM THE RADIUM CENTRE., JUTLAND, AARHUS (CHIEF: PROF. CARL KREBS, M. D.)

INVESTIGATION INTO THE TIME FACTOR IN THE ROENTGEN IRRADIATION OF CANCER CELLS[1]

Protraction Experiments with a Transplantable Mouse Round-Cell Sarcoma and a Transplantable Mouse Carcinoma

by

B. Refslund Poulsen

The purpose of the present work is to investigate the time factor in the irradiation of cancer cells. As protraction offers the clearest experimental conditions, only its effects have been examined.

In the majority of the time-factor experiments made hitherto with biological objects the effect of protracted or fractional irradiation has been demonstrated as being less when compared with short, single irradiation, provided that the difference in the time-distribution has been sufficiently great. The smaller effect is explained as an incomplete cumulation on account of regeneration during irradiation (in case of protraction) or between individual irradiations (in case of fractioning).

However, certain apparently reliable investigations have been published, showing that there has been greater effect from the protracted or fractional dose compared with short, single irradiation.

SCHINZ & SLOTPOLSKI, for example, found that when irradiating rabbit testes there was a greater effect from fractioning the dose when the period of regeneration after depopulation of the vas deferens was applied as a criterion of the effect. In explanation these authors use the term "Roentgen allergy".

In an isolated reaction, inhibition of mitosis in tissue culture from chicken embryo, SPEAR & GRIMMET found greater effect from a certain intensity (about 11 r/min.) than from any higher or lower intensity, and thus demonstrated a so-called "critical intensity".

Earlier work by SPEAR et al. and by JUUL & KEMP had shown that mitosis inhibition becomes operative in the pre-mitotic stage and in no other — that in other words there is a sensitive stage in the cell cycle to this particular reaction.

A critical intensity for the lethal effect of roentgen has also been demonstrated. MOTIDA & ADATI irradiated yeast cells for a period longer than the duration of the cell cycle and found an optimum effect at a certain intensity. For example, using the same dose they could obtain twice as great an effect with a lower intensity of 56 r/min. than

[1] Submitted for publication, Febr. 12, 1945.

with a higher intensity of 111 r/min. The authors ascribed the increased effect at the low intensity to the occurrence of a sensitive stage in the cell cycle. At the optimum intensity (56 r/min.) the intensity on the one hand was so slight that the cell division, regarded as a single reaction, was able to proceed, but on the other hand it was sufficiently great for the lethal effect in the sensitive stage. Then, by extending the time of irradiation over a period longer than that of the cell cycle, the cells passed through the sensitive stage during irradiation, and increased effect was observed.

Of more recent experiments, BAUER when irradiating rabbit bone marrow found an increased effect when the dose was protracted and fractioned. The criterion employed was the cell density in the sections after irradiation compared with unirradiated marrow.

Features common to the objects for which increased effect was found from the time-diffusion of the dose, are a high frequency of cell division and, with the exception of yeast cells, high sensitivity.

As stated, the most frequently demonstrated form of time-factor activity is an effect which decreases with increasing protraction. Particularly beautiful and thorough protraction experiments showing this form of time-factor effect on various objects have been made by SIEVERT & FORSSBERG. These authors found an S-shaped curve for the protraction when the effect was plotted along the ordinate, the irradiation time (at the same dose) logarithmically along the abscissa. The threshold value of the decreasing effect was found at a lower intensity with objects with a high frequency of cell division than with objects with a low frequency.

Material and Technique

For the experiments I elected to use mouse transplantation tumours, as these can be employed for procuring an ample and, as far as possible, homogeneous material. After a number of tentative experiments it was found that the reduction of takes after irradiation and the prolongation of the latent period for the development of the tumours were the only practical criteria of the irradiation effect.

On account of the relation which, in view of the foregoing, was to be anticipated between the time-factor on the one hand, and the frequency of cell division and sensitivity on the other, two essentially different tumours were chosen for the time-factor experiments: one a rapidly growing, more sensitive *round-cell sarcoma*, the other a slowly-growing, more resistant *carcinoma*.

The round-cell sarcoma has been employed for many experimental investigations at the Radium Centre at Aarhus, where the tumour has been retransplanted since 1928. The carcinoma has been retransplanted at the same institution since 1932. Both tumours since 1937 have been continued on the same stock, a non-inbred stock, descended from a brother and sister pair in 1937. This stock has since not been crossed with other stocks.

The *carcinoma*, named Krebs' Carcinoma No. 2, is histologically a Carcinoma solidum with fairly abundant mitoses. Like most transplantation tumours after subcutane-

ous inoculation it grows in a rounded, sharply delimited mass with a distinct capsule. When the unirradiated carcinoma is transplanted there is constantly 100 per cent. of takes and no spontaneous regression.

The *round-cell sarcoma* has received various names from the different authors. Histologically the individual cells are of the size of lymphocytes. The nucleus is round, occupying the greater part of the cell, so that the cytoplasm forms merely a narrow basophile margin around it. Mitoses are abundant. There is little stroma. Investigations by BICHEL seem to suggest that the cells are of myeloid origin. After subcutaneous inoculation from unirradiated tumour the round-cell sarcoma grows in a vaguely delimited flat layer without a capsule. Moreover the tumour has a strong tendency to generalize, as there often are perivascular accumulations of tumour cells in the organs, and even organs that apparently are free of metastases are capable of giving takes after transplantation (KAALUND-JØRGENSEN).

Unlike the carcinoma, the unirradiated round-cell sarcoma does not give 100 per cent. of takes, but it has an average of 95 per cent. from operative transplantation. The percentage is also liable to fluctuate over a long period (from 90 to 98 per cent.). Finally, the round-cell sarcoma shows considerable spontaneous regression, as an average of 25 per cent. of the tumours developed disappear spontaneously.

Whereas the carcinoma a priori seemed suitable for quantitative roentgen-biological experiments, the round-cell sarcoma has a number of inherent drawbacks. That this less suitable tumour nevertheless was chosen for the experiments was due to the desire to examine just this form of cancer cell which, on account of its relatively great sensitivity and rapid growth, was expected to offer unusual features with regard to the time factor.

First a number of tentative experiments were made with the two tumours. Only progressively growing tumours were employed. By this means it was possible to establish the take curves, which, as with previously tested tumours, were S-shaped. For the carcinoma the curves were found to be independent of whether the tumour was irradiated in vivo or in vitro, and whether a lead shield was placed round the tumour or irradiation was universal. Furthermore, the percentages of takes from the individual tumours showed but little statistical spreading with this form. As regards the round-cell sarcoma, however, there were a number of difficulties which had to be surmounted before the tumour could be used for quantitative experiments. These difficulties were:

1) The transplantability of the non-irradiated tumours is not quite 100 per cent., and indeed the percentage fluctuated over a long period. Over a continuous series of 10 passages the percentage does not fluctuate more than might be fortuitous. But if a series of passages is examined one or two months later, the average percentage of takes may have altered (though not more than between 90 and 98). This means that an experiment must be carried through with single continuous passages and preferably with tumours from the same passage, as indeed is done in the protraction experiments (see later).

2) Generalization of the lesion. The effect of this is that local irradiation of the tumour with a lead screen round it is inapplicable. If the tumour is localized to the axilla and only the animal's hindquarters are covered up, takes continue to come from the irradiated tumour tissue even after 7,000 r, whereas the so-called "lethal-dose" when irradiating in vitro is about 3,500 r. The reason must be that from the organs under the lead there flows a constant stream of viable tumour cells which in the transplantation are transferred with the killed tumour tissue. It was therefore necessary to make the irradiation universal; this is practicable, as at the doses here employed (between 1,000 and 2,000 r), the animals die only after four or five days, by which time the symptoms of roentgen injury (anæmia, leucopenia) become manifest.

3) There is a rather high spontaneous recession. This must suggest that the stock employed was not "pure" in respect of this tumour. In all probability, spontaneous recession is the reason why with this tumour after irradiation there is great statistical spreading of the percentage of takes from the various tumours. For instance, if a series of tumours are given a middle dose — at which the greatest variations of the effect are obtained (the takes-curves are S-shaped) — there is a much greater diffusion than with non-irradiated tumours. Thus for 11 tumours grown by means of transplantation from three groups of sister-tumours, the results after universal irradiation with a dose in the neighbourhood of the middle dose were:

Group	I			II				III			
No. of surviving transplanted animals	17	20	18	20	19	18	18	19	18	19	19
No. of animals with takes	8	9	0	7	10	1	2	12	8	9	12
Percentage of takes	47	45	0	35	53	6	11	63	44	46	43

Total result $\frac{78}{205} = 38\ \%$.

In this series there are 3 strikingly low percentages (0, 6 and 11) which lie beyond what can be accidental. It is probable that these low percentages of takes are due to the respective tumours being in a state of incipient spontaneous recession; for it is well-known that tumours in spontaneous recession take badly (Woglom). Thus even if as in these experiments one always endeavours to select tumours with rapid, progressive growth, the above table shows that the exclusion of these "bad" tumours is impossible.

While on the subject of spontaneous recession it should be mentioned that the spontaneous recession of the tumours which developed after transplantation of the irradiated tumours did not affect the results of the experiments. In the great majority of cases the recession does not occur until the tumour has reached about cherry size, so that it is so to say always possible to confirm the take before the tumour recedes. Therefore the spontaneous recession of the daughter tumours does not affect the take percentages, and indeed in all the experiments it proved to be the same relatively whether the mother tumour was irradiated or not.

The statistical spreading of the take percentages from the individual tumour was so great that the transplantability of the individual tumours could not be employed for quantitative experiments. It was therefore necessary to devise a new method.

The method worked out on the basis of the above experience is briefly as follows: For one experiment a large number of tumour animals was employed, being divided into groups of equal size. The tumour pulp from each group was mixed and transplanted subcutaneously to a large number of untouched animals. Accordingly, the reduction of the take-percentage and the prolongation of the latent period for the development of the tumours from the irradiated groups in relation to an unirradiated control group is an expression of the irradiation effect.

The details of the experimental arrangements are as follows: All tumours used in one experiment had grown from transplantation from the same cell mixture. This is procured by mincing and mixing several progressively growing tumours, and for each experiment twice as many animals were inoculated as were required for the experiment.

From among these a selection was made of the animals whose tumours were growing most rapidly and progressively, and from these again were taken the required number, as far as possible selecting animals with tumours of the same size and consistence. The animals were divided in arbitrary order into groups of 16. Accordingly, all tumours employed in an experiment were of the same age, all progressively growing and as far as possible of the same size and consistence.

The tumour cells were irradiated by means of a universal exposure of the tumour animals. These were placed loose in a thin-walled, round wooden box, 17 cm. in diameter, which is the largest area over which it is possible to ensure homogeneous intensity in the irradiation field. The height inside this box is only 2.5 cm., so that the animals cannot lie over one another. The cover consists of thin celluloid, the absorption of which is infinitesimal. Both sides and cover are perforated for ventilation.

The 16 animals can be placed in this chamber without difficulty; and, as most of them have never previously been confined together, they are in constant movement; and if the temperature in the room is kept above 20°, the animals do not crowd together to sleep during the long exposures. While being exposed the box with the animals is placed on two thin wooden rods 50 cm. from the floor, which is screened with lead.

After irradiation the tumours are removed from each group separately, an equal quantity being taken from each of the 16 animals. These pieces of tumour are minced with scissors and thoroughly mixed in a Petri-dish. The cell mixture from each group is transplanted to 100 fresh animals, the idea being through this large number to equalize the statistical spreading that is due to the genetic differences of the various animals in relation to the tumour tissue (the stock employed not being "pure" in respect of this tumour). As a sufficient number of animals of the same age cannot be procured for each experiment, each group of 100 is allotted an equal number of the same age (the age difference, however, was not more than one month). Each group contained half males and half non-pregnant females.

The tumour pulp was transplanted subcutaneously in the right axilla with a graduated screw-syringe, with which one can inject exactly the same volume into each animal. About 1/20 c. c. of the tumour pulp (one turn) was injected into each animal.

The transplanted animals were inspected every second or third day. The experimental period was three months, after which period scarcely any more tumours appear. All animals with a definitely palpable tumour were reckoned as takes.

When calculating the take-percentage it must be borne in mind that a number of animals die without reaction before all the tumours have appeared. Leaving out all these animals would incorrectly displace the take-percentage in a positive direction, as most takes occur during the early part of the experimental period. It was therefore elected to leave out of consideration only those animals that die before half of the tumours had appeared. This point of time can be read on the following curves for the latent period.

This experimental technique being quite new, it was necessary to determine the limits of error prior to making the protraction experiments. Accordingly, two irradiation experiments were made with the round-cell sarcoma — the tumour giving rise to the greatest uncertainty, and the dose chosen was the middle dose. By means of preparatory experiments this was found to be about 1,160 r.

Two experiments were made with 4 groups in each, irradiation proceeding under the conditions later employed at the highest intensity in the protraction experiments (filter 0.5 Cu + 1 Al, distance 50 cm., 175 kw., 25 ma. Intensity 58 r/min.).

For reasons of clarity the latent period of the tumours (the time elapsing from transplantation till the tumours are definitely palpable) is shown graphically. Along the abscissa is plotted the number of animals after transplantation, along the ordinate the number of tumours appearing, expressed as a percentage of the total number. The numerical expression of the latent period employed is the mean latent period (the time elapsing from transplantation till half of the tumours have developed).

Experiment 1.

Transplantation result and latent period for the round-cell sarcoma. Four groups of tumour mice from the same passage irradiated with 1,160 r at the intensity 58 r/min. at 50 cm. Transplantation performed 24 hours after irradiation.

No. of surviving animals	81	86	92	86
No. of animals with takes	36	47	50	46
Take percentage	44.4	54.7	54.4	53.5
Mean latent period in days	ca. 16	ca. 16	ca. 17	ca. 16

Latent period in Exp. 1. (Fig. 1.)

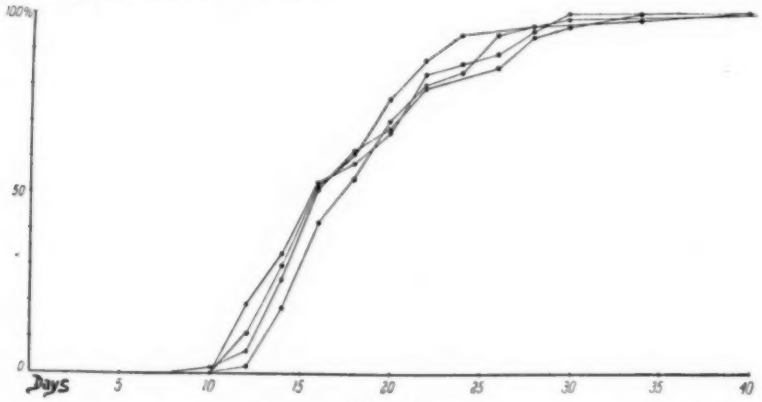

Fig. 1.

Abscissa: Number of days after transplantation.
Ordinate: Number of tumours, expressed as a percentage of the total number.

Experiment 2.

Repetition of Exp. 1.

No. of surviving animals	86	86	85	84
No. of animals with takes	39	42	46	39
Take percentage	45.4	48.8	54.2	46.5
Mean latent period in days	ca. 15	ca. 16	ca. 16	ca. 16

Latent period in Exp. 2. (Fig. 2.)

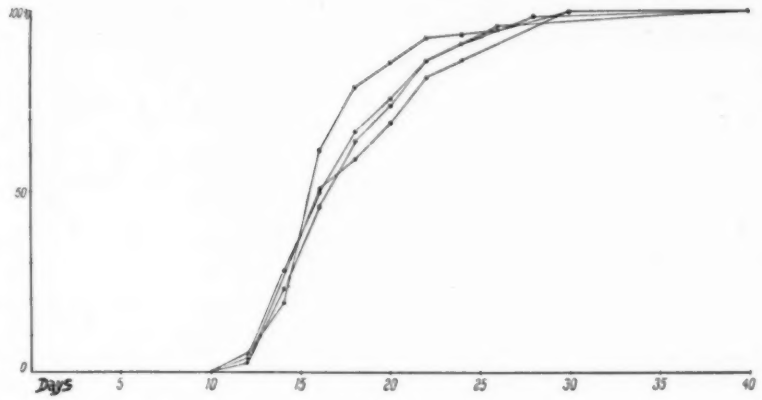

Fig. 2.

Abscissa: Number of days after transplantation.
Ordinate: Number of tumours, expressed as a percentage of the total number.

In these two experiments the takes vary from 44 to 55 per cent. and from 45 to 54 per cent. The 8 take-percentages vary with a standard deviation of 4.4 per cent., which is lower than the Bernoulli standard deviation with 85 animals in every experiment (5.4 per cent). The standard deviation of the difference between two take-percentages is 7.7 per cent.

The agreement in respect of the latent period is obviously good.

No estimation was made of the reliability of the carcinoma on the same lines as with the round-cell sarcoma, as this more constant and non-generalizing tumour must a priori be expected to give more certain results, as in fact will appear from the protraction experiments.

Protraction Experiments

The protraction experiments were performed with the middle dose, at which a difference in the effect causes the greatest reaction, the S-shaped take-curve being steepest with the middle dose. For the purpose of being able to vary the intensity as required a Philips Maximus T-apparatus was used, this being able to work with high amperage. The object being one of large extent, a distance of 50 cm. had to be allowed in order to ensure homogeneous intensity over the entire field of irradiation. The highest intensity obtainable at this distance was 58 r/min.

When determining the maximum time for which irradiation could be continued, consideration had to be given both to apparatus and to

animals. It was found that an exposure time of 24 hours at low intensity was practicable without injury to the apparatus. A preliminary test showed that the animals were quite capable of tolerating 24 hours in the irradiation chamber if they were provided with a little water-soaked white bread. Furthermore it had appeared from the tentative experiments that the palpatory recession of the irradiated tumours of the round-cell sarcoma after the dose employed did not set in until after 2 days, the degenerated cells (see later) evidently being replaced the first time by tissue fluid. 1 r/min. was therefore chosen as the lowest intensity.

The number of points determinable between these two limits of intensity depended on the number of animals obtainable and the volume of the work involved, as each experiment, as already stated, had to be completed at once with tumours from one and the same passage. The line had to be drawn at 4 groups for irradiation and one unirradiated control group. After SIEVERT & FORSSBERG the 4 irradiation periods were fixed according to a logarithmic scale, the period being almost quadrupled at each reduction of the intensity. The figures were slightly adjusted to practical requirements.

The conditions under which the exposures were made were: Tension 175 kw., filter 0.5 Cu + 1 Al. The dose employed was the middle dose, which by this method was found to be *1,160 r for the round-cell sarcoma and 1,600 r for the carcinoma.*

Intensity r/min.	58	12.3	3.3	1.0
Milliamperes	25	6.5	6.5	4
Distance cm.	50	50	97	139
Exposure time for round-cell sarcoma, min.	20	94	351	1,160
Exposure time for carcinoma, min.	28	130	485	1,600

The system employed in selecting tumour animals and transplantation animals was the same as in Experiments 1 and 2. All the various groups of tumour animals (apart from the fact that the controls were not irradiated and that the exposures were given with different intensities) were subjected to the same conditions, except that the interval between exposure and transplantation could not be standardized in these experiments, and therefore any influence this may have had to be investigated separately (see below).

In each experiment the exposures were made in immediate succession and in the order shown.

Prior to the experiments very careful measurements were taken in order to ensure that the physical dose under the given conditions was the same at each intensity. For instance, the output of the apparatus was tested with a Küstner dosimeter before and after each experiment without the apparatus having been switched off in the meantime. Further,

the intensity was determined direct at the various distances by means of a Hammer dosimeter; and finally, the intensity during all exposures was likewise checked with a Hammer dosimeter, of which the chamber was pushed into the margin of the cone of the rays.

Experiment 3.

Transplantation result and latent period for round-cell sarcoma after irradiation with 1,160 r at various intensities and transplantation 28 hours after commencement of the irradiation, as well as a non-irradiated control group.

Intensity r/min.	58	12.3	3.3	1.0	non-irradiated control
No. of surviving animals ...	90	93	96	94	92
No. of animals with takes..	40	40	46	5	92
Take percentage	44	43	48	5	100
Mean latent period, days ...	ca. 16	ca. 18	ca. 17	ca. 19	5

Latent period in Exp. 3 (Fig. 3).

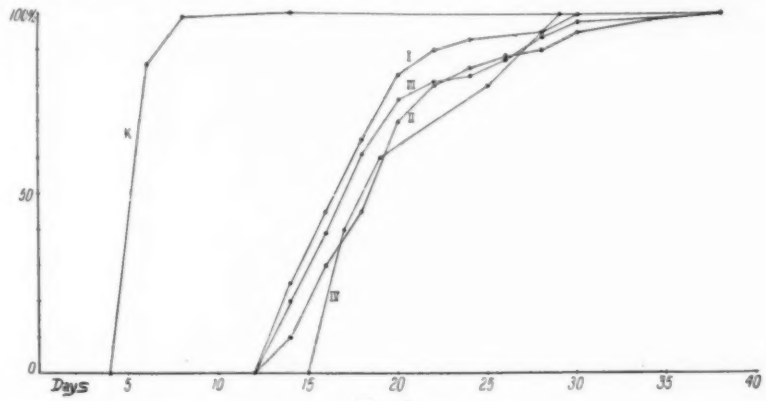

Fig. 3.

Abscissa: Number of days after transplantation.
Ordinate: Number of tumours, expressed as percentage of the total number.

I 58 r/min.
II 12.3 »
III 3.3 »
IV 1.0 »
K non-irradiated control.

As will be seen, the result of the irradiation was unchanged at the three highest intensities, whereas at the intensity 1 r/min. there is a much lower percentage of takes and a rather longer latent period (the latter is somewhat uncertain on account of the small number of tumours).

All the irradiated animals were subjected to the same conditions apart from the intensity differences, except that in all cases the same time elapsed from the *beginning* of the exposure until transplantation, which means that the interval between the *conclusion* of the exposure and transplantation is different for the various groups. In order to shut out this latter possible source of error, and partly in order to confirm the result, the experiment was repeated at the two extreme intensities, but with transplantation at both intensities performed partly immediately and partly 24 hours after the conclusion of the exposure.

Experiment 4.

Transplantation result and latent period for round-cell sarcoma after irradiation at 1,160 r at the highest and lowest intensities, followed by transplantation immediately and 24 hours after termination of the irradiation as well as a non-irradiated control group.

Intensity r/min.	58	58	1	1	non-irradiated control
No. hours between end of irradiation and transplantation	0	24	0	24	
No. animals surviving	95	96	94	94	93
No. animals with takes	48	43	22	23	91
Take percentage	51	45	23	24	98
Mean latent period, days	ca. 15	ca. 16	ca. 18	ca. 18	5

Latent period in Exp. 4 (Fig. 4).

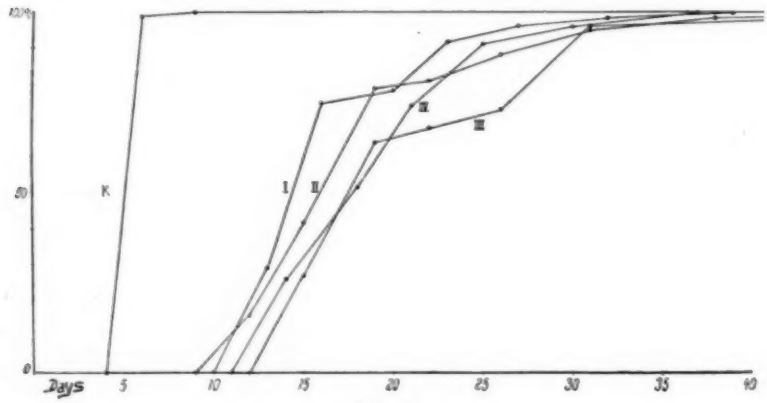

Fig. 4.

Abscissa: No. of days after transplantation.
Ordinate: No. of tumours expressed as a percentage of the total number.

I 58 r/min., transplantation immediately after end of irradiation.
II 58 » » 24 hours » » » »
III 1 » » immediately » » » »
IV 1 » » 24 hours » » » »
K non-irradiated control.

It will be seen that in this experiment too there is a greater effect at the low intensity than at the high, regardless of the interval between irradiation and transplantation.

This observation was additionally confirmed by two more experiments, arranged as in Exp. 4. In both experiments, however, the percentage of takes as a whole was lower than usual — involving a somewhat greater diffusion of the results — due to the fact that the tumours were not fully capable of taking. All the same, the experiments show the same as Exp. 3 and 4 — a greater effect at the lower intensity.

The results of the protraction experiments with the round-cell sarcoma were as follows: The percentage of takes is not affected by variations of the intensity from 58 r/min. to 3.3 r/min. At the intensity of 1 r/m., however, there is increased effect. This is surprising, as one would anticipate a smaller, or perhaps unchanged effect from protracting the dose. There can be no doubt about the increased effect, because it was observed in 4 experiments. The absolute value of the difference in the effect between long and short irradiation varies somewhat in the different experiments, but at the middle dose it is at least about 25 per cent and thus is an increase of really significant extent.

At an intensity of 1 r/min. the mean latent period is lengthened by about two days compared with the mean latent period at the other intensities (Exp. 4). Thus the increased effect is also observable in the latent period.

Both take-percentage and latent period are unaffected by a 24 hours' prolongation of the interval between irradiation and transplantation.

The protraction experiments with the *carcinoma* were carried out in the same manner as with the round-cell sarcoma. As this tumour shows no marked tendency to generalize, it was not necessary to employ universal irradiation; but as the animals cannot tolerate being pegged out so long as the protraction of the dose requires, universal irradiation was also employed for the carcinoma. With the method of exposure employed the middle dose was found to be 1,600 r. With the carcinoma the transplantation was performed at only two junctures: immediately and 24 hours after the termination of the irradiation; apart from this the technique of the experiment was the same as with the round-cell sarcoma in Exp. 3 and 4.

Experiment 5.

Transplantation result and latent period for carcinoma after irradiation with 1,600 r at various intensities and with transplantation 24 hours after termination of the irradiation, as well as a non-irradiated control group.

Intensity r/min.	58	12.3	3.3	1	non-irradiated control
No. of surviving animals	93	89	91	93	99
No. of animals with takes	53	54	65	71	97
Percentage of takes	57	61	71	76	98
Mean latent period, days	ca. 17	ca. 15	ca. 15	ca. 13	ca. 7

Latent period in Exp. 5 (Fig. 5).

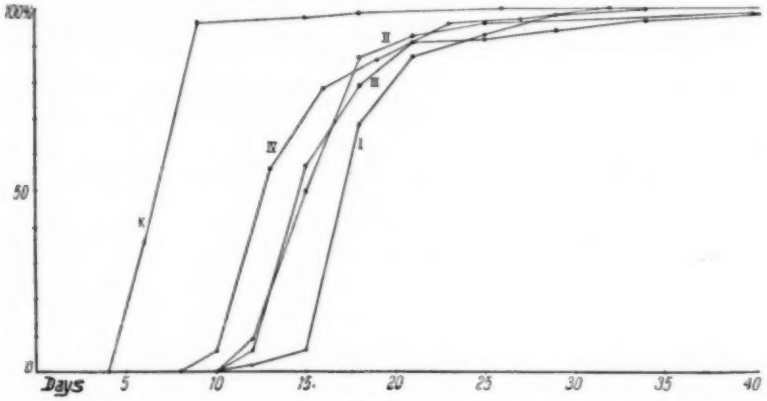

Fig. 5.

Abscissa: Number of days after transplantation.
Ordinate: Number of tumours, expressed as a percentage of the total number.

I 58 r/min.
II 12.3 »
III 3.3 »
IV 1.0 »
K non-irradiated control group.

Experiment 6.

Transplantation result and latent period for carcinoma after irradiation at highest and lowest intensities and transplantation immediately and 24 hours after termination of the irradiation, as well as a non-irradiated control group.

Intensity r/min.	58	58	1	1	non-irradiated control
No. of hours between end of irradiation and transplantation	0	24	0	24	
No. of surviving animals	93	92	86	80	96
No. of animals with takes	47	47	54	56	96
Percentage of takes	51	51	63	70	100
Mean latent period, days	ca. 19	ca. 16	ca. 13	ca. 11	ca. 6

Latent period in Exp. 6 (Fig. 6).

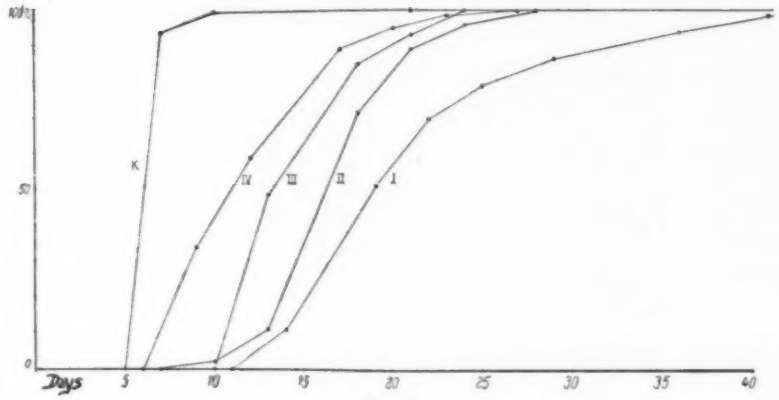

Fig. 6.

Abscissa: Number of days after transplantation.
Ordinate: Number of tumours expressed as a percentage of the total number.

I 58 r/min. Transplantation immediately after end of irradiation.
II 50 » » 24 hours » » » »
III 1 » » immediately » » » »
IV 1 » » 24 hours » » » »
K non-irradiated control group.

As will be seen, after irradiation the carcinoma shows an evenly decreasing effect with increasing protraction, amounting to about 20 per cent., when the intensity is varied from 58 r/min. to 1 r/min. Nor is it certain that the percentage of takes with this tumour is affected by the time of transplantation.

The latent period is prolonged with increasing protraction, whereby the mean latent period at 1 r/min. is only about half of the period at 58 r/min.

It is also observable from Exp. 6 that the latent period is dependent on the time of transplantation, the mean latent period being shortened when transplantation is made 24 hours after irradiation, in contrast to what happens when it is made immediately after irradiation. The explanation of this phenomenon is simple when it is remembered that the effect, seen after irradiation, at the moment of observation is the result of the original irradiation effect less the regeneration that has proceeded in the period between irradiation and the moment of observation. In the transplantation method the moment of observation is identical with the time of transplantation. Therefore, the fact that the latent period is shortened when transplantation is made 24 hours after irradiation means that a regeneration has commenced in that special reaction or

reactions, of which the lengthening of the latent period after irradiation is the expression.

For the carcinoma, the latent period in the development of the non-irradiated tumours is only short compared with that of the round-cell sarcoma (6—7 days as against 5 days). This slight difference would seem to suggest that the difference in growth-energy of the two tumours is very small. In actual fact, however, the difference is much greater, because, owing to the delimited form of growth of the carcinoma, the take can be recognized much earlier than with the round-cell sarcoma. The carcinoma, as already stated, grows in a rounded, collective mass and therefore can already be palpated with certainty when it is about the size of a small pea. The round-cell sarcoma, on the other hand, grows in the form of a flatly infiltrating, diffusely margined layer, with the result that a take cannot be recognized with certainty until it has attained a size of about 1 cm. in diameter. By this time about 3 to 4 times as much tumour tissue has been formed as in the case of a carcinoma at a corresponding time. When it is furthermore remembered that the cell-density in a round-cell sarcoma section is considerably greater than in a carcinoma section (see photos Nos. 1 and 4), so that per volume unit of round-cell sarcoma there are many more cells than per volume unit of carcinoma, it is clear that the cell-division frequency of the round-cell sarcoma compared with that of the carcinoma must be considerably higher than is suggested by the latent period in the development of the two tumours.

Similarly, the difference in the middle dose of the two tumours observed with this method of irradiation (about 500 r) is no true expression of their respective sensitivities. For example it may be observed that irradiation in vitro revealed a difference of 700 r in the middle dose. The smaller difference resulting from the method of irradiation employed must be explained by the different macroscopic modes of growth of the two tumours, with a consequent difference in the diffusion of the rays in the body of the mouse and the tumour.

Histological Changes in Irradiated Tumours

As according to earlier investigations the time-factor must be assumed to stand in a certain relation to the cell cycle and mitotic activity, the tumours were examined histologically for the number of mitoses and degeneration phenomena after irradiation. The histological picture being a varied one from tumour to tumour and in the different parts of the same tumour, no exact count is possible. For this reason only indubitable changes are recorded here. As a rule, each observation is based upon sections of 5 tumours.

On making histological examinations at varying times after a brief single irradiation it was found that there was a marked difference in the form of reaction of the two tumours after irradiation. Both tumours were examined after rising doses with intervals of 500 r.

Round-cell sarcoma. After only two hours there were pronounced signs of degeneration, manifested by widespread nuclear pycnosis (see photo No. 2). After 24 hours the greater part of the degenerated cells had disappeared, and it is possible to demonstrate a distinct diminution

Micro-Slides

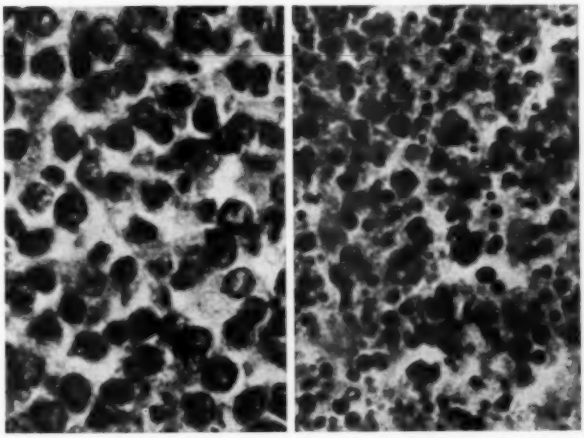

Photo 1. Photo 2.

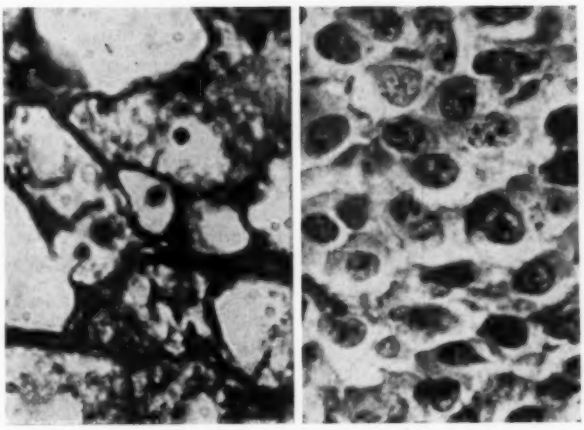

Photo 3. Photo 4.

Photo 1. Section of the non-treated round-cell sarcoma. Hematox.-Eosin. Ca. 800.
Photo 2. Round-cell sarcoma 6 hours after irradiation with 2,000 r. Strong nuclear pycnosis. Ca. 800.
Photo 3. Round-cell sarcoma 51 hours after irradiation with 3,000 r. Foot's silver impregnation. The naked stroma remains after the degenerated cells have disappeared; only here and there in the meshes a few remaining tumour cells. Ca. 800.
Photo 4. Carcinoma, non-irradiated. Ca. 800.

of the cell density in the slide (photo No. 3). These changes are already strongly assertive in the lowest examined dose, 500 r, and would undoubtedly be demonstrable at even lower doses.

This rapid form of reaction has been observed with other round cells, e. g. by POHLE & BUNTING with rat-spleen lymphocytes, where signs of degeneration were demonstrable after only 5 r, and with lymphosarcomata in man (STRUNGE).

The mitoses disappear totally after 500 r and more in the course of 2 hours, to reappear after 24 hours.

On the other hand, in the *carcinoma* there are no signs of degeneration four days after irradiation, not even after 4,000 r. No mitoses were found 6 and 10 hours after irradiation, whereas they were observed again after 24 hours (no examination made in the interval).

In the case of irradiation with low intensity (1 r/min.) the tumours were examined at 5 hour intervals up to 70 hours after irradiation began. As regards the *round-cell sarcoma*, mitoses were found in such abundant numbers during and after 19 hours irradiation that their number, judged approximately, could not be said to be reduced. This proves that the cycle is not interrupted by this intensity.

A curious phenomenon was observed some time after irradiation terminated: 36 hours after the commencement of the exposure there was a larger number of mitoses than normal. Whereas one finds 1 to 2 mitoses per field in non-irradiated tumours when examined with the immersion lens, 5 to 6 and often more were found in the same field 36 hours after commencing irradiation with the low intensity. The explanation must be that some inhibition of the mitoses must nevertheless have taken place during irradiation, now manifested by an accumulation of the mitoses that had been retarded but then released, plus the mitoses that were not inhibited.

With protracted irradiation the degeneration phenomena are not markedly manifest until 70 hours after irradiation commences, there then being a distinct reduction of the cell density.

In the case of the *carcinoma*, mitoses were present during and after the protracted irradiation, except 10 hours after the commencement of the exposure. No explanation can be advanced as to why the cycle stops during the first part of the exposure but is resumed during the remainder of it. The same phenomenon by the way has been observed by other authors (ROBERTSON). With the *carcinoma* no sign of degeneration was observed during the first 70 hours after irradiation began.

If we compare the histological picture of the round-cell sarcoma with the takes-curve, we can form an impression of what reactions are expressed in the takes-percentage and the lengthening of the latent period. The increasing nuclear pycnosis in the round-cell sarcoma when the dose is increased must mean that the takes-curve is mainly a mortality curve, or rather a survival curve, as a take subsequent to irradiation is dependent on the number of surviving cells in the transplant. On the other hand, the latent

period for the development of a tumour, which is the time elapsing from transplantation until the tumour is palpable, must express the velocity at which the cells succeed in dividing in sufficient numbers until a palpable tumour is established. Therefore, the latent period must chiefly be an expression of the growth energy. This explains that for the carcinoma the time of transplantation has an influence on the latent period of the tumour, but not definitely on the percentage of takes, as regeneration sets in earlier for reduction of the growth energy, which is a reversible process, than for the reduction of the takes, which is dependent on the number of viable cells, for which process regeneration is presumably slower.

Discussion

The result of the protraction experiments can be set up graphically as in Fig. 7.

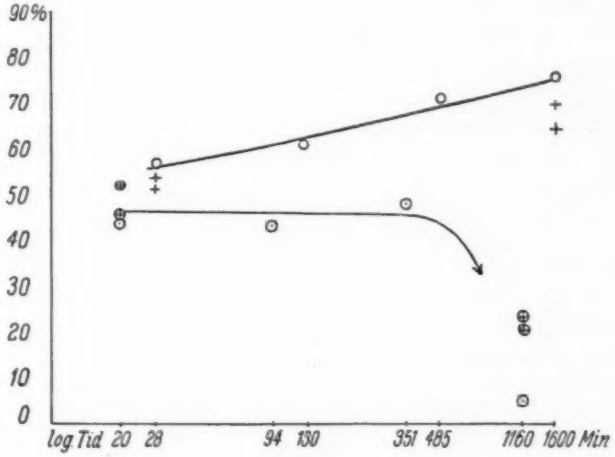

Fig. 7.

Ordinate: Takes percentage.
Abscissa: Irradiation time with logarithmic scale.
For carcinoma the dose is 1,600 r, for round-cell sarcoma 1,160 r.

○ Carcinoma . . . . . chief experiment.
\+ » . . . . . repeated »
⊙ Round-cell sarcoma . . . chief »
⊕ » » . . . repeated »

The round-cell sarcoma shows unchanged effect from the intensity of 58 r/min. to 3.3 r/min., but at intensity 1 r/min. we get increased effect. At what intensity the maximum of the increased effect lies is a question that is left unsettled by the experiments, due to the afore-

mentioned difficulties. Nevertheless, these experiments show that the fall of the curve is of a significant order.

It is obvious that with increasing protraction the effect will again decrease at some still lower intensity viz. when the influence per time unit becomes so slight that the regeneration exceeds the injury. Thus with the round-cell sarcoma a critical intensity has been demonstrated, situated round about 1 r/min.

The carinoma, on the other hand, shows a steadily decreasing effect with increasing protraction and thus displays a form of time-factor effect so familiar from numerous other objects, one that is explained as an incomplete cumulation on account of regeneration during irradiation.

The cause of the increased effect at the crit cal intensity is scarcely explicable unless we presuppose a temporarily increased sensitivity of the cells. This temporarily increased sensitivity may a) be due to a normal phase in the cell cycle or b) be induced by the irradiation.

a) The critical intensity may be explained, as the above quoted authors SPEAR & GRIMMET, MOTIDA & ADATI have done, by the assumption of a sensitive phase in the cell cycle. In that case the critical intensity must be so low that the cell cycle can proceed, and this again must be manifested by the mitoses not being inhibited — or only slightly — at this intensity. The fact that the histological investigations reveal mitoses during and after irradiation at the low intensity supports the theory of the sensitive phase in the cell cycle as the cause of the critical intensity, but it is not proof.

It is scarcely practicable to demonstrate a sensitive phase in the cell cycle in a population of cells which are in various stages of the cycle. But in young egg cells (frog eggs, ascaride eggs, sea-urchin eggs), in which the cycle in the first divisions proceeds synchronously, a sensitive phase seems definitely demonstrated (i. a. LUTHER).

The fact that no critical intensity has been shown for the carcinoma may be due either to the time of irradiation being insufficiently long, or that the sensitivity in the hypothetical sensitive phase is not sufficiently high in proportion to the sensitivity outside that phase, or perhaps that the phase is too brief.

b) The other explanation, that the increased sensitivity is caused by the irradiation, presupposes certain properties in the particular species of cell that displays critical intensity. In the first place we must assume that the latent period for the irradiation effect on the object is of a suitable length; in the second place, we must assume that during the maximum of the irradiation effect the cell shows increased sensitivity.

If we imagine that in the beginning of a long irradiation a cell receives one or several non-lethal hits, it causes a molecular displacement

in the cell structure — the so-called primary effect. This involves secondarily a disturbance in the physio-chemical balance of the cell, which after a varying time leads to the so-called "roentgen disease". It is not unreasonable to think that during the maximum of this "roentgen disease" the cell is more labile to a new influence, that in other words the sensitivity of the cell is increased in this phase. If the latent period for the roentgen disease is of a suitable length in proportion to the time of irradiation — longer than the irradiation time at a high intensity, and shorter than the irradiation time at the critical intensity — and if later during the long exposure the cell receives one or more new hits within the sensitive phase induced by one or more of the first hits, the result will be a greater injury than if the cell were subjected to the same number of hits during a short period of irradiation. Such a mode of action is particularly likely in the case of labile cells with little power of regeneration such as those of the round-cell sarcoma.

In reality the difference between the two theories is slight, as they both presuppose a phase of increased sensitivity. According to the first theory (a) this phase is a normally occurring one in the cell cycle; according to the other (b) it is a state that is induced by the irradiation.

Neither of the two theories can be proved or disproved by the present investigation; but the latter one is a better working hypothesis as a basis for further time-factor studies in fractioning.

SUMMARY

Protraction experiments have been made with two mouse-transplantation tumours: a rapidly growing, sensitive round-cell sarcoma, and a slowly-growing, resistant carcinoma. The criterion of the effect was the percentage of takes and the latent period for the development of the tumours. The investigations were carried out with a new experimental method which gives great statistic reliability.

The objects were irradiated with the middle dose at the intensities of 58—13.3—3.3 and 1 r/min.

In the case of *carcinoma* there was found (expressed both by the percentage of takes and by the latent period) a steadily decreasing effect with increasing protraction. The percentage of takes falls about 20 per cent. when the intensity is varied from 58 r/min. to 1 r/min. The latent period for the development of the tumours was decreased at 1 r/min. to about the half of what it was at 58 r/min.

The *round-cell sarcoma* shows unchanged effect when the intensity is varied from 58 r/min. to 3.3 r/min., but at 1 r/min. there is a distinctly increased effect, the percentage of takes in the two experiments being lowered by at least 25 per cent. This increased effect is also observable in the latent period for the development of the tumours.

The decreasing effect on the carcinoma with increasing protraction is easily explained as an incomplete cumulation as a result of regeneration during irradiation.

The increased effect of a low intensity on the round-cell sarcoma must be assumed to express that at this intensity (round about 1 r/min.) a critical intensity has been de-

monstrated, as with steadily increasing protraction the effect must again decrease at some low intensity or other.

Two hypotheses are advanced in explanation of the critical intensity.

ZUSAMMENFASSUNG

Protrahierungsversuche mit zwei Mäusetransplantationstumoren: einem schnellwachsenden, sensiblen Rundzellensarcom und einem langsamwachsenden, resistenten Carcinom, sind vorgenommen worden. Kriterien der Wirkung waren das prozentuale Angehen und die Latenzzeit für die Entwicklung der Tumoren. Die Untersuchungen sind mit Hilfe einer neuen Versuchsmethode angestellt worden, die eine grosse statistische Sicherheit leistet.

Die Tumoren sind mit Mitteldosis bei den Intensitäten 58 — 13.3—3.3 und 1 r pr. Minute bestrahlt worden.

Sowohl das prozentuale Angehen wie auch die Latenzzeit zeigt bei dem Carcinom eine regelmässig abnehmende Wirkung bei zunehmender Protrahierung. Das prozentuale Angehen nimmt mit ungefähr 20 % ab, wenn die Intensität von 58 r pr. Minute bis 1 r pr. Minute variiert wird. Die Latenzzeit für die Entwicklung der Tumoren ist bei 1 r pr. Minute ungefähr die Hälfte der Latenzzeit bei 58 r pr. Minute.

Das Rundzellensarcom zeigt eine ungeänderte Wirkung, wenn die Intensität von 58 r/Min. bis 3.3 r/Min. variiert wird, aber bei 1 r/Min. zeigt sich eine deutlich gesteigerte Wirkung, indem das prozentuale Angehen in zwei Versuchen mit mindestens 25 % abnimmt. Diese gesteigerte Wirkung lässt sich auch bei der Latenzzeit für die Entwicklung der Tumoren spüren.

Die abnehmende Wirkung auf das Carcinom bei zunehmender Protrahierung lässt sich zwanglos als eine unvollständige Kumulation in folge der während der Bestrahlung eingetretenen Regeneration erklären.

Die zunehmende Wirkung auf das Rundzellensarcom bei niedriger Intensität zeigt, da die Wirkung bei irgend einer niedrigen Intensität wieder abnehmen muss, die Existenz einer kritischen Intensität, und zwar in der Nähe der Intensität 1 r/Min.

Zwei Hypothesen zur Erklärung der kritischen Intensität werden aufgestellt.

RÉSUMÉ

On a expérimenté l'irradiation, avec protraction de la dose, de deux sortes de tumeurs greffées sur des souris, dont un sarcome globucellulaire, sensible et à croissance rapide, et un carcinome résistant et à croissance lente. Les critères de l'effet obtenu ont été, 1) le pourcentage des greffes positives, et 2) le temps qui se passe entre la transplantation et le développement des tumeurs, la période d'incubation. Les recherches ont été faites à l'aide d'une nouvelle méthode expérimentale, qui offre une grande sécurité statistique.

Les tumeurs ont été irradiées à dose moyenne aux intensités suivantes: 58 — 13.3 —3.3 et 1 r par minute.

Pour le carcinome, et le pourcentage des greffes et la période d'incubation montrent un effet graduellement décroissant pour la protraction progressive. Le pourcentage des greffes positives diminue de 20 % environ, correspondant à une variation d'intensité de 58 r par minute jusqu'à 1 r par minute. La période d'incubation n'est à 1 r par minute que la moitié environ de ce qu'elle est à 58 r par minute.

Le sarcome globocellulaire montre un effet stationnaire pour une variation d'intensité de 58 r par minute jusqu'à 3.3 r par minute, mais à 1 r par minute une augmen-

tation de l'effet apparait nettement, puisqu'à deux expériences le pourcentage des greffes s'abaisse de 25 % au moins. Cette augmentation de l'effet se fait sentir aussi bien par la période d'incubation.

L'effet décroissant sur le carcinome par rapport à la protraction progressive s'explique de façon naturelle comme une accumulation incomplète par suite de la régénération qui se fait pendant l'irradiation.

L'effet croissant sur le sarcome globocellulaire qui accompagne la diminuation d'intensité montre l'existence d'une intensité critique, à savoir l'intensité d'un r par minute environ, étant évident qu'à partir d'un certain point une diminuation ultérieure de l'intensité doit s'accompagner d'un décroissement de l'effet.

L'auteur forme deux hypothèses pour expliquer l'intensité critique.

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ON OSTEOARTHROSIS ALKAPTONURICA (OCHRONOTICA) WITH DESCRIPTION OF ONE CASE[1]

by

Johan Hertzberg

The main clinical importance of alkaptonuria with ochronosis consists in the lesion it provokes in bones and joints, the so-called osteoarthrosis alkaptonurica (ochronotica). This lesion is rare. It was described first by VIRCHOW in 1866. Subsequently some other authors have referred single cases, as a rule examined anatomically (see the references). The correlation between alkaptonuria and osteoarthrosis was recognized first by ALBRECHT and ZDAREK in 1902, the pathogenesis explained by UEBERMUTH and others, and the roentgenological picture by BAUER and KIENBOCK.

A brief description shall first be given of the pathogenesis of the disease. The ochronotic pigment is deposited in the articular cartilage, especially in old cartilage, with poor metabolism. This becomes black, loses its elasticity, becomes brittle, and shows little resistance to mechanical strain. The cartilage cracks easily, and small black fragments of cartilage are wrenched off into the joint, where they soon become attached to the synovial membrane, gradually becoming firmly affixed to this and embedded. This particularly takes place on the more »quiet» parts of the joint, thus in the knee joint in the posterior recesses. The deposit of cartilage in the synovial membrane is easily observed due to the black colour of the cartilage.

The cartilage fragments act upon the synovial membrane, and a synovial reaction occurs with hyperemia and secretion of more synovial fluid. The synovial membrane is thickened, as also subsequently the entire articular capsule. Granulation tissue, poor in cells, and new vessels are formed around the pieces of cartilage. For a long time the cartilage remains lying as »dead bodies» in the synovial membrane. They

[1] Submitted for publication, Febr. 12, 1945.

may gradually become absorbed, however, and disappear. Protrusions also appear on the synovial membrane. In these cartilage may be formed secondarily, turning them into ecchondroses (GONNERMANN). It may happen also, probably by calcium deposits, that capsular osteomas are formed, which is shown by the present case.

The cartilage regenerates in spite of the wear (the dissection, UEBERMUTH), and can preserve its normal height for a long time. Gradually, however, the wear may become overwhelming, and the height of the cartilage is reduced, ultimately it may even disappear, so that the bone lies bare. Mechanical action then causes changes in the articular surfaces of the bone, with sclerosis, in other parts with formation of cysts, small infractions, and so forth. The subchondral bone marrow is irritated, proliferates and grows into the diseased cartilage. Marginal exostoses are also formed. Pigmented cartilage is reported to be able to become forced up into the marrow cavity, there being surrounded by growing granulation tissue (KLEINSCHMIDT). The cartilage may disappear entirely, and bony ankylosis then occurs.

Several investigators also have reported the presence of osteoporosis in this disease, anatomically as well as roentgenologically. The pigment is deposited in the osseous system, much less, however, than in cartilage. The spicules become narrower and thinner, and the marrow spaces wider. A typical lacunar resorption occurs. These patients frequently are subject to fractures as a result of minor injuries.

Thus with regard to the joint lesion it is the articular cartilage which is involved first. The lesion here causes secondary changes in the articular capsule and the articular surfaces. The cartilaginous lesion in ochronosis excites considerable interest because it is an unusually distinct example of sloughing of diseased cartilage, which is wrenched off, and then absorbed by the synovial membrane, causing synovitis. The dark colour facilitates the perception of the fragments of cartilage in the articular capsule.

The deposit of ochronotic colouring matter is specific, and according to UEBERMUTH the cartilage injury is absolutely characteristic of this disease, and is most suitably termed a dissection (Chondrosis dissecans ochronotica). Also in other joint diseases, however, such as deforming arthrosis, patellar chondromalacia, and others, there occurs a sloughing off of cartilage, which is then embedded in the synovial membrane and causes synovitis (HULTÉN and GELLERSTEDT).

Even if the cause of the articular lesion is specific, the morbid processes greatly resemble those observed in ordinary deforming osteoarthrosis.

Case history

A. F., 54 year old fisherman. Admitted July 9., discharged August 12. 1942. Previously healthy, until two years ago he commenced having pain in the left shoulder, which thereupon started becoming stiff. One year ago the right shoulder also became stiff and painful. The stiffness in these joints subsequently has increased, and he has felt pain, particularly in cold weather, and this has partly been an impediment to his work as a fisherman. Two to three months ago he also developed pain in both knees, and he had a swelling on the outside of the right knee. This has not been painful. The knees have become slightly stiff.

General examination, July 9. 1942

He is in moderate condition, and of healthy appearance. Afebrile. Sedimentation rate 12 mm. Heart, lungs and abdomen: No abnormal findings. *The shoulders:* Atrophy of all muscles of the shoulder arch on both sides. He is able to elevate both arms to the horizontal. This movement, however, takes place only by swinging the scapula. Complete ankylosis is present in both shoulder joints. *The spine:* Slight scoliosis, loss of the physical curve of the lumbar spine. Normal movement, without pain. *Right knee:* Slight swelling and some fluid in the joint. Some degrees missing of full flexion and extension. No pain on movement. On the lateral aspect of the joint, close to the patella, an oval, bone-hard tumour, slightly over the size of a nut, is felt. To a certain extent it is movable, and appears to be affixed to the articular capsule.

No changes were found in the other joints.

It was then remarked that his urine, which had been allowed to stand during the night, had turned dark brown. Analysis demonstrated: Neutral reaction, specific gravity 1.026, albumin, blood and pus negative. Haines' solution was reduced, the fluid at the same time turning dark. Freshly voided, pale urine with addition of an alkalizing agent, when shaken produced a dark colour. By addition of a week solution of ferric chloride a rapidly transient blue colour was obtained. Thus a definite alkaptonuria was present.

Renewed examination of the patient disclosed that he had a blue-black, translucent colour of the cartilages of the ears, and that the sclerotics of both eyes had black spots laterally. The skin in both axillae was dark-coloured. He also gave information that he had noticed that the urine turned dark when left standing for any length of time. Thus he had a typical ochronosis. Wasserman test negative.

Roentgenological examinations

Right shoulder: Extensive deforming osteoarthrosis with flattening of the humeral head. The articular cartilage has disappeared almost completely. Big exostoses occur at the margins of the articular facets, to the greatest extent caudally. In the bone around the joint is seen sclerosis and rarefactions, and this extends into the humeral head and shaft. Especially the small rarefactions in the humeral shaft are remarkable, as they are said to be pathognomonic for the disease (KIENBØCK). *Left shoulder:* The same findings, only to a lesser degree (fig. 1). *Right knee:* Osteoporosis around the joint. Usual width of the cartilaginous space between femur and tibia, but reduced between femur and patella. All the bones show exostoses on the articular surfaces. Subchondral sclerosis in the patella. On the lateral aspect of the patella there is a »free body», the size of a date kernel, and another one, equally large, posteriorly in the joint, as also a smaller one posteriorly superiorly. *Left knee:* Similar changes are observed here, though only one smaller »free body» posteriorly superiorly (fig. 2).

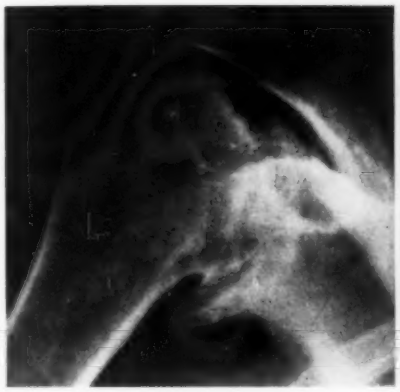

Fig. 1 a.

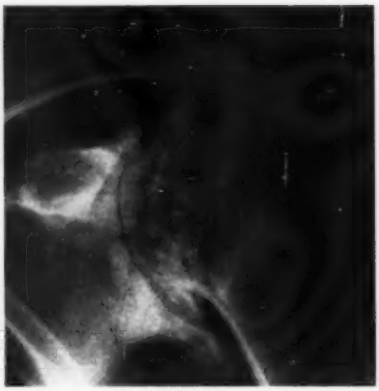

Fig. 1 b.

The spine: Distinct osteoporosis. Moderate scoliosis. The normal lumbar lordosis is completely lost. The intervertebral disks are abnormally narrow, and in some places absent on the concave side of the scoliosis. The disks show peculiar calcifications in the whole spine. They form horizontal stripes, mostly two, through the disks. This is also called »patchy condensation» of the disks. On some vertebras are seen marginal exostoses of moderate degree. Calcification of the lumbar vertebral ligaments is also observed (fig. 3—5).

Pelvis: No particularly abnormal findings in the sacrum, iliosacral joints and hips. The cartilage in the hips is preserved. The foremost part of the pelvis is sclerotic. In the prostatic glands calcifications are seen.

Apart from the humeral changes mentioned, the long bones do not clearly demonstrate any features characteristic of ochronosis.

Under local anesthesia extirpation was performed of the free body in the right knee. The osseous body palpated laterally to the patella was removed through a small incision. It was firmly affixed to the articular capsule, and had to be cut loose. Some articular fluid escaped through the small opening, and it was noticed that the articular cartilage was dark. The body removed was bone-hard throughout, greyish white with separate dark brown spots.

Microscopy (EKER): Spicules of ordinary tissue with a spongious appearance, and further several irregularly placed small cells. Between the cells moderately cellular connective tissue. Accumulation in several places of brown pigment, partly in the bone spicules, partly in the connective tissue.

Diagnosis: Exostosis with brown pigmentation.

The case distinctly demonstrates the affection and following destruction of the articular cartilage and the intervertebral disks, characteristic of the cases of osteoarthrosis alkaptonurica recorded hitherto. The changes involve many joints and the whole spine. The identical changes are largely found as those present in deforming osteoarthrosis, only to a higher degree. But some of the findings are peculiar. In the

Fig. 2 a—d.

Fig. 3.

shoulders the destruction of the articular cartilage is great, and the exostoses bigger than usual in plain osteoarthrosis. The most noticeable finding in the knees are the large capsular osteomas, which will probably have to be correlated to the capsular osteomas existing in ordinary osteoarthrosis, however markedly extensive. The formation of these has probably not yet been fully elucidated. In the spine, the patchy condensation of the intervertebral disks is characteristic.

Diffuse osteoporosis is also present in large parts of the skeleton.

Fig. 4.

Fig. 5.

In the humeral shaft small circumscribed defects are scattered all over the bone, similar to the finding described by KIENBOCK in his case.

The clinical symptoms are distinct, and fairly great, though they are somewhat less than the anatomical symptoms. The lesion has caused ankylosis of the shoulders. In the knees the symptoms of synovitis are predominating, as well as the capsular osteomas. The great changes in the spine cause little clinical symptoms. Even though the disease develops slowly, and must be stated to have a benign course, it will frequently, as in this case, ultimately result in the patient becoming more or less of an invalid.

The roentgenologic picture must be said to be fairly characteristic, and perhaps sufficient for the establishment of the diagnosis. As the clinical symptoms with the urinary findings are pathognomonic, however, the diagnosis is established probably always in connexion with the clinical examination.

SUMMARY

After a short review of the pathogenesis of osteoarthrosis alkaptonurica, a case of this disease is described and its most characteristic features are pointed out.

ZUSAMMENFASSUNG

Nach einem kurzen Bericht über die Pathogenese bei Osteoarthrosis alkaptonurica wird ein Fall dieser Krankheit beschrieben und ihre wichtigsten Besonderheiten hervorgehoben.

RÉSUMÉ

Après une courte description de la pathogénie d'ostéoarthrosis alkaptonurica, un cas de cette maladie est décrit, et son signe caractéristique est marqué.

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